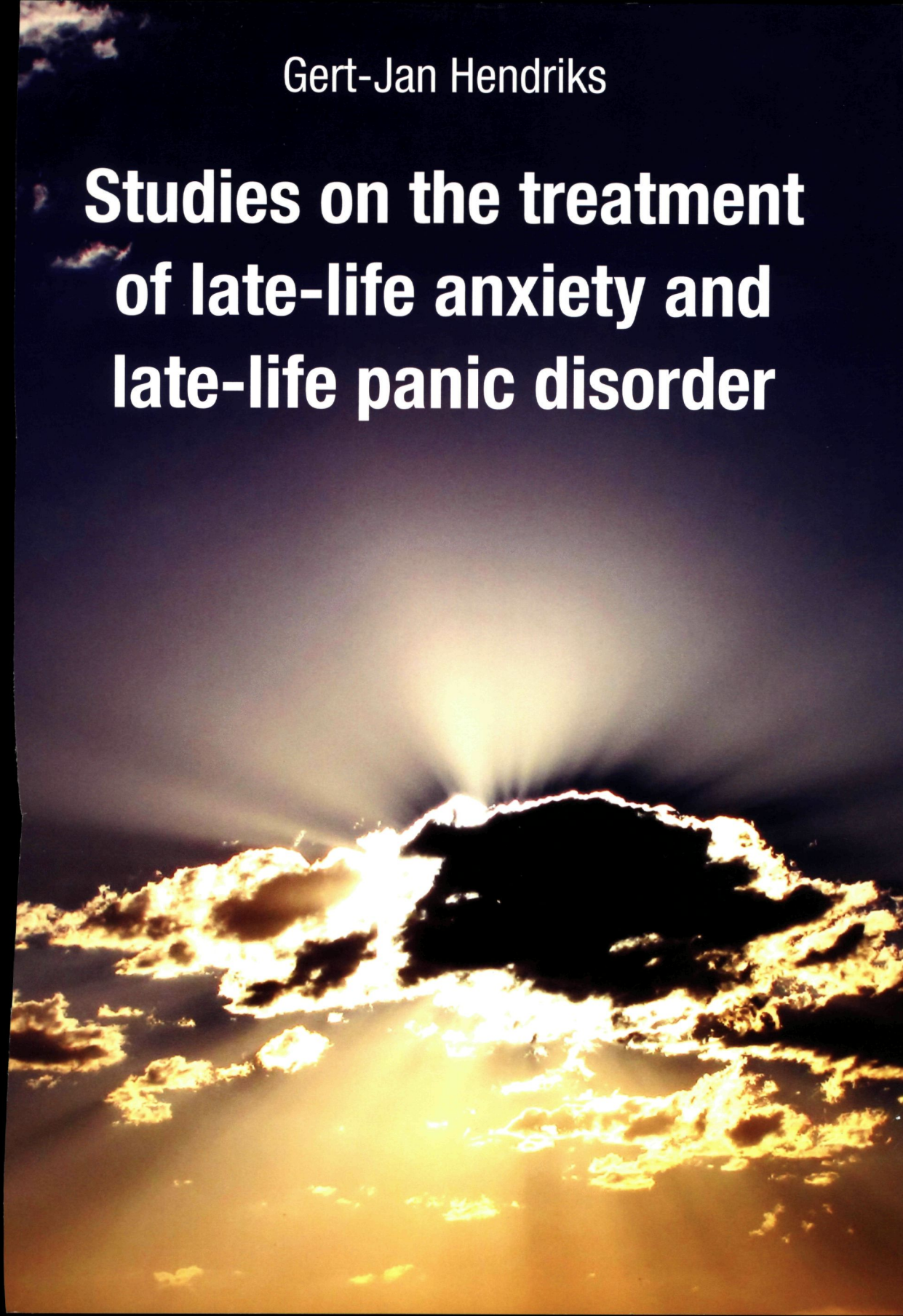
Gert-Jan Hendriks

Studies on the treatment of late-life anxiety and late-life panic disorder



Verzorging omslag: Roberto van Zwieten, info@yourr.nl
Verzorging binnenwerk: H&R Communicatieve Vormgeving, Purmerend
Drukwerk: Wilco, Amersfoort
Publicatie: Uitgeverij Boom, Amsterdam

The research in this thesis was funded by an unrestricted research grant by GlaxoSmithKline.
The financial support of the publication of this thesis by the Board of Directors of Pro Persona is gratefully acknowledged.
Hendriks & Roosenboom is gratefully acknowledged for their financial support.

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Een wetenschappelijke proeve op het gebied van de
Sociale Wetenschappen

Proefschrift

ter verkrijging van de graad van doctor
aan de Radboud Universiteit Nijmegen
op gezag van de rector magnificus prof. mr. S.C.J.J. Kortmann,
volgens besluit van het College van Decanen
in het openbaar te verdedigen op dinsdag 1 december 2009
om 13.30 uur precies

door

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geboren 23 april 1960
te Elst (Gld.)

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Voor mijn ouders

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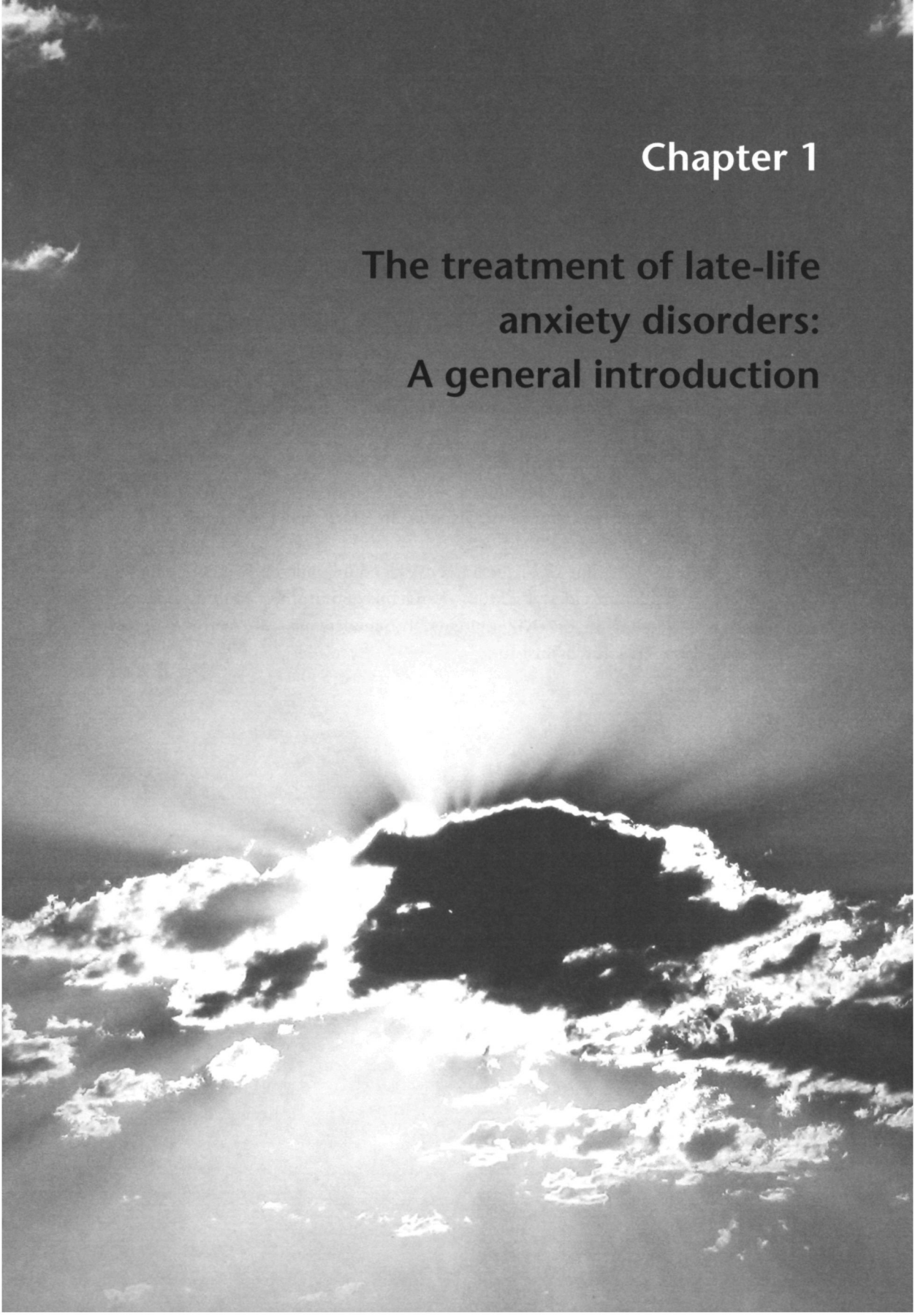

Chapter 1

The treatment of late-life anxiety disorders: A general introduction

This chapter is based on:

- Hendriks, G.J., Keijsers, G.P.J. & Hoogduin, C.A.L. (1999). Cognitieve gedragstherapie bij ouderen met angststoornissen – casusbeschrijving [Cognitive behavioural therapy in late-life anxiety – case study]. *Tijdschrift voor Psychiatrie, 41*, 677-681.
- Hendriks, G.J. & Weijnen, I. van (2001). Angststoornissen [Anxiety disorders] In: T.J. Heeren, M.G Kat & M.L. Stek (red.), *Handboek Ouderenpsychiatrie* (pp. 97-107). Maarssen: De Tijdstroom.
- Hendriks, G.J., Allart-van Dam, E. & Balkom, A.J.L.M. van (2004). Waarom is kennis over therapieresistentie bij angststoornissen belangrijk? [Why is knowledge about treatment failure in anxiety disorders important?]. In: G.J. Hendriks & J.L. Klompenhouwer (red.). *Angststoornissen: behandeling en therapieresistentie* (pp. 1-23). Nijmegen: Cure & Care Publishers.
- Hendriks, G.J., Rees, M.M. van, Keijsers G.P.J., Verbraak, M.J.P.M. & Hoogduin, C.A.L. (2008). Behandeling van ouderen met een obsessieve compulsieve stoornis [Treatment of obsessive-compulsive disorder in older patients – case studies]. *Tijdschrift voor Psychiatrie, 50*(9), 617-621.
- Multidisciplinaire Richtlijn Angststoornissen Addendum 'ouderen' [Guideline anxiety disorders – addendum elderly] (2008). Landelijke Stuurgroep Multidisciplinaire Richtlijnontwikkeling in de GGZ (auteurs: J. Schuurmans, M. Veerbeek & G.J. Hendriks). Utrecht: Trimbos-instituut.

1.1 Introduction

For young and middle-aged adults powerful, evidence-based and guideline-recommended treatments are available for panic disorder with (PDA) or without agoraphobia (PD), social phobia, obsessive-compulsive disorder, posttraumatic stress disorder, and generalized anxiety disorder (Abramowitz, 1997; Bakker, Van Balkom & Spinhoven, 2002; Bisson & Andrew, 2007; Bradley, Green, Russ, Dutra & Westen, 2005; Fedoroff & Taylor, 2001; Mitte, 2005a, Mitte, 2005b; Norton & Price, 2007; Seidler & Wagner, 2006; Stein, Seedat, Van der Linden & Zungu-Dirwayi, 2000; Taylor, 1996; Van Balkom, Bakker, Spinhoven, Blaauw, Smeenk & Ruesink, 1997; Van der Linden, Stein & Van Balkom, 2000). Cognitive-behavioural therapy (CBT) and pharmacotherapy with selective serotonin reuptake inhibitors (SSRIs) are the treatments of choice for these disorders. CBT and SSRIs are also assumed to be effective in older adults diagnosed with anxiety disorders (Pinquart & Duberstein, 2007). However, to date empirical evidence on the efficacy of these two treatments in adults aged 60-plus years is scarce since randomized controlled trials (RCTs) testing both CBT and SSRIs and direct comparisons of the two treatment arms in older and younger adults are lacking. Inspired by successful outcomes following CBT as well as SSRIs in case studies of 60-plus patients suffering from anxiety disorders (Hendriks, Keijsers & Hoogduin, 1999; Hendriks, Van Rees, Verbraak, Keijsers & Hoogduin, 2008b), the main purpose of this thesis was to gather empirical evidence for the effectiveness of these two treatments in this specific population.

In this chapter the available evidence on the prevalence, onset and course of late-life anxiety disorders, the phenomenology and impact of anxiety in later life, and the effectiveness of CBT and antidepressants in the management of the various disorders is described. If available, for each of these aspects data on differences and similarities between older and younger adults diagnosed with the same anxiety disorder are also summarized.

The following case history illustrates the effectiveness of CBT in an older adult who had been suffering from nervousness, panic attacks and avoidance behaviour for several decades.

> *Mr. P was 69 years old when he was referred to our outpatient anxiety clinic. For over 40 years he had been suffering from stomach aches, tension headaches, palpitations, tremors, dizziness, nervousness, fear of fainting and heart disease, constant worries about his health and finances, and had avoided numerous circumstances and activities (e.g. crossing bridges, visiting crowded places, and travelling long distances). On occasions*

he used oxazepam PRN[1] to alleviate his fears and tension; when he had to visit friends or family living in another town, for example, he took oxazepam in advance to dampen the symptoms of anxiety and worrying during travelling. He had consulted his general practitioner (GP) almost monthly for years requesting a physical examination. Each visit his GP reassured him that he was healthy and that his complaints were attributable to nervousness and tension, for which he prescribed benzodiazepines. Eventually, Mr. P was referred to our outpatient clinic on account of his chronic worries and nervousness.
Using the Anxiety Disorders Interview Schedule–IV (Bouman, De Ruiter & Hoogduin, 1997; DiNardo, Brown & Barlow, 1994) Mr. P was found to meet all criteria for panic disorder with agoraphobia (PDA), for which he had never received treatment. He was subsequently referred to protocolized, PDA-specific CBT. After having concluded the 14-week programme, oxazepam PRN was tapered off and then stopped consistent with the last exposure step. Following treatment Mr. P was considerably better able to control his panic symptoms and his agoraphobic avoidance was reduced to almost zero.

This case history of an older man with PDA illustrates the effectiveness of CBT in spite of the 40-year chronicity. However, in elderly people reporting anxiety-related complaints the symptoms may often not be recognized as serious and the possibility of a psychological disorder is hence most often overlooked, leaving many patients un(der)diagnosed and un(der)treated. The diagnostic focus often primarily concerns the patient's physical problems and the reassurance that no physical abnormalities have been found. Even if diagnosed adequately, the elderly patient is seldom offered a targeted and evidence-based treatment. Thus, rather than antidepressants and/or CBT, the treatments of choice for anxiety disorders, benzodiazepines are prescribed.

In contrast to the abundance of empirical research on depression and dementia in the elderly and even though research into the treatment of late-life anxiety disorders has stepped up in recent years, it is still in its infancy and there still is a large gap to bridge (Flint, 2005a; Flint, 2007) Studies on age-related differences in anxiety phenomenology are limited and well-conducted RCTs in elderly patients are still scarce. In their multidisciplinary guidelines for the treatment of anxiety disorders, the National Institute for Mental Health (i.e. Trimbos-instituut) proposes in the appendix on the elderly ('Addendum Ouderen', 2008)[2] several possible reasons explaining this lack of research. First, depression and dementia are both considered 'pure' geriatric psychiatric disorders.

1 PRN = pro re nata ('when it occurs' or 'if necessary')
2 http //www ggzrichtlijnen.nl/

The age at onset of both depression and dementia is usually considerably higher and may therefore be more easily recognized than late-life anxiety disorders. In contrast, anxiety disorders generally have an earlier onset and a more chronic and fluctuating course into late adulthood. Second, in later life comorbidity with depression may mask the existing anxiety symptoms, increasing the likelihood that the anxiety disorder goes unrecognized. Also by virtue of focusing on somatic symptoms, especially chronic conditions like pulmonary or cardiovascular diseases, clinicians may miss an underlying or comorbid anxiety disorder in elderly patients. In addition, 'ageism', which in this context refers to the misinterpretation of deviant behaviours as age-appropriate, may hinder the diagnosis and thus proper treatment of late-life anxiety disorders. Avoidance behaviour after a myocardial infarct is, for instance, often deemed understandable and an adequate, adaptive response. Finally, being retired and often receiving support in and around the home, elderly people may increasingly and successfully avoid anxiety-provoking situations, like travelling by car or visiting crowded shopping malls unattended, without raising suspicions of a more serious affliction.

With the proportion of young and middle-aged adults with anxiety disorders receiving adequate treatment generally varying between 15 to 50% (Wang, Lane, Olfson, Pincus, Wells & Kessler, 2005b), undertreatment of this type of disorders can be said to be rather common. Belonging to an older age group, however, is an additional risk factor for not receiving adequate treatment (Wang, Berglund, Olfson, Pincus, Wells & Kessler, 2005a). Thus, the scarcity of empirical research in this age group may partly also be attributable to the fact that we are dealing with a population that tends to go largely underdiagnosed and hence un(der)treated. Both from an economic and a mental health-perspective the cost of this unmet need is substantial. Recent studies estimate that 'years lived with disability' would decrease with 49% and treatment costs with 40% if every person suffering from an anxiety disorder would be offered timely and optimal treatment (Andrews, Issakidis, Sanderson, Corry & Lapsley, 2004; Issakidis, Sanderson, Corry, Andrews & Lapsley, 2004). Although it is not realistic to expect every person suffering from an anxiety disorder to be offered such adequate treatment, these figures should make us think given that our life expectancy is increasing and thus also the number of and the time elderly patients are left untreated. The few figures and recommendations we do have all suggest that both at the diagnostic and the therapeutic level as well as from a scientific point of view our elderly citizens that suffer from anxiety symptoms merit more attention and care.

One may believe that because older people that suffer from anxiety are generally underdiagnosed and hence not referred for targeted treatment, anxiety disorders are a minor health problem in later life. With the work presented in this thesis this

presumption is challenged and the need for more empirical research in this specific field substantiated. The following sections provide an overview of the empirical status of late-life anxiety disorders and various prejudices are refuted. Several of the many questions that have so far remained unanswered are tackled in the eight studies that follow and that form the body of the present dissertation. These eight studies are introduced at the end of this chapter. Two investigated late-life anxiety disorders in general. Four studies were specifically aimed at establishing the efficacy and feasibility of guideline-recommended treatments for late-life panic disorder and two studies were aimed at differences in CBT efficacy and agoraphobic cognitions between older and younger patients. Therefore the empirical findings on the specific domain of late-life panic disorder are highlighted.

1.2 Late-life anxiety disorders remain largely underdiagnosed and un(der)treated despite their high prevalence

Recent epidemiological studies identified anxiety disorders as the most prevalent of all mental disorders in later life. Comprising more than 3,000 participants aged between 55 and 85 years, the Longitudinal Aging Study Amsterdam (LASA; see http://www.lasa-vu.nl/ for more detailed information) found a six-month prevalence of approximately 10% for late-life anxiety disorders (Beekman, Bremmer, Deeg, Van Balkom, Smit, De Beurs et al., 1998; Van Zelst, De Beurs, Beekman, Deeg & Van Dyck, 2003). Additionally, the National Comorbidity Survey Replication (NCS-R), carried out in 9,000 adults (over 18 years) in the United States, estimated the overall life-time prevalence of anxiety disorders in later life at more than 15% (Kessler, Berglund, Demler, Jin, Merikangas & Walters, 2005a). Although data from the NCS-R conducted in the United States reported a declining life-time prevalence of anxiety disorders in adults aged over 60 years relative to the younger adults, in both age groups anxiety disorders were the most prevalent mental disorders. In contrast, underdiagnosing and undertreatment are reflected in the available epidemiological data The LASA data showed that a mere 2.6% of elderly patients reporting anxiety symptoms consulted a psychiatrist and only 3.8% were seen by health professionals at a mental health outpatient clinic. The use of antidepressants was also deplorably low (3 8%), while 25% were prescribed benzodiazepines (De Beurs, Beekman, van Balkom, Deeg, Van Dyck & Van Tilburg, 1999). Although six years later the use of benzodiazepines had increased to 43%, the other figures had only marginally changed. The prescription of antidepressants had doubled to 7% and referral to mental health facilities risen to 14% (Schuurmans, Comijs, Beekman, De Beurs, Deeg, Emmelkamp et al., 2005). Compared to depression, the referral rate to specialized mental health care for late-life anxiety disorders was three times lower, i.e. 55% versus 17% (Ettner & Hermann, 1997).

The NCS-R confirmed the increased overall risk of elderly people (aged over 60 years) going untreated for mental disorders relative to their younger counterparts: the odds ratios for receiving specialized mental health care were 2.4 to 4 8 larger in the younger adults (Wang et al., 2005b).

1.3 Although partially overlapping, later-life anxiety disorders and depression need to be distinguished

That in the elderly, although prevalent, anxiety disorders are generally un(der)treated may strengthen mental health professionals and researchers in their assumption that in later life depression is much more common than anxiety. This conclusion does not hold. However, LASA reported a one-month prevalence of 2% for major depression and a rate of 12.9% for minor depression (Beekman, Deeg, Van Tilburg, Smit, Hooijer & Van Tilburg, 1995). The NCS-R mentioned life-time prevalence rates of 10 6% and 1.3% for major depression and dysthymia, respectively (Kessler et al., 2005a). With a six-month prevalence of approximately 10% in LASA and a life-time prevalence of approximately 15% in the NCS-R it is concluded that the two classes of disorders are equally prevalent in the elderly.

In addition, the widespread assumption that anxiety accompanies depression at an older age and that for late-life anxiety a diagnosis of a mixed anxiety-depression syndrome is to be preferred to a diagnosis of distinct anxiety disorders (Flint, 1994, Flint, 2005a), may not be warranted. The LASA also revealed that with 1.8% the prevalence of a mixed anxiety-depression syndrome was lower than previously assumed (Schoevers, Beekman, Deeg, Geerlings, Jonker & Van Tilburg, 2000). Instead, and although there was clear evidence of a large overlap, the study uncovered more differences than similarities between late-life anxiety and depression (Beekman, De Beurs, Van Balkom, Deeg, Van Dyck & Van Tilburg, 2000). Whereas a quarter of the elderly participants diagnosed with an anxiety disorder also met the DSM-IV criteria for a comorbid major depression, approximately half of those diagnosed with major depression satisfied the criteria for a comorbid anxiety disorder. Although anxiety and depressive symptoms partially overlapped, they could also be distinguished from each other, while the risk factors for the two syndromes were also distinct. Whereas late-life depression was associated with an older age of onset and an external locus of control, the risk profile for late-life anxiety disorders was more complex and consisted of a combination of vulnerability factors, actual stress and social aspects. These differences in comorbidity patterns and risk factors suggest that also in later life anxiety and depression are distinguishable diagnostic entities meriting separate investigation.

1.4 Late-life anxiety disorders characteristically have an onset at a relatively young age and run a chronic course

The NCS-R data showed that, when compared to mood disorders, anxiety disorders generally have the youngest age at onset (Kessler et al., 2005a). The median age of onset was 11 years, with 75% of all anxiety disorders starting before the age of 21 years and only 1% starting after the age of 65 years, whereas for mood disorders the median age at onset was 30 years with 75% starting before the age of 43 years. Although prospective post-treatment follow-up studies in adult populations (18 to 65 years) gauging the clinical course of anxiety disorders for more than ten years are scarce, evidence has been gathered revealing the chronicity of symptoms and relative high relapse risk for anxiety disorders in general and for panic disorder in particular (Andersch & Hetta, 2003; Bruce, Yonkers, Otto, Eisen, Weisberg, Pagano et al., 2005; O'Rourke, Fahy, Brophy, Prescott, 1996; Rubio & Lopez-Ibor, 2007; Rubio & Lopez-Ibor, Jr., 2007; Swoboda, Amering, Windhaber & Katschnig, 2003; Tyrer, Seivewright & Johnson, 2004; Yonkers, Bruce, Dyck & Keller, 2003). The recovery rate for anxiety disorders following treatment varied from 40 to 60%, but with the same proportions the relapse rates during follow-up periods of several years remained high. More specifically, with 0.82 versus 0.48 the probability of recovery of PD was higher than that of agoraphobic PD, while the probabilities of relapse were similar (0.56 and 0.58, respectively; Bruce et al., 2005).

Given that the greater majority of adults suffering from anxiety disorders do not receive adequate treatment (Wang et al., 2005b) and that for those that do the chance of relapse is still as high as 0.4 to 0.6, we can safely conclude that anxiety disorders tend to start at a young age and are highly likely to be chronic, running a fluctuating course into late adulthood, thus contributing to a relatively high prevalence in later life. Nevertheless, some critical remarks are warranted here. With regard to the clinical course of the disorders, empirical findings on recovery and relapse were, to date, naturalistic and observational, and not obtained using guideline-recommended treatments. More importantly, treatment was mainly limited to pharmacotherapeutic interventions with benzodiazepines, SSRIs or tricyclic antidepressants (TCAs), or combinations of these agents. In only one study (Tyrer et al., 2004) psychological and pharmacological treatments were delivered concurrently. Moreover, as most studies reported data on adherence to treatment, lack in adherence may also contribute to the chronic course of many anxiety disorders.

1.5 Late-life anxiety disorders should not be regarded as a minor health problem

Clinicians and researchers are inclined to consider anxiety disorders in older adults a minor health problem that does not seriously impair their quality of life, but the reverse is true (Wetherell, Thorp, Patterson, Golshan, Jeste & Gatz, 2004a) Firstly, as mentioned earlier, empirical findings showed serious comorbidity late-life anxiety disorders are frequently associated with major depression and other anxiety disorders (Beekman et al , 2000, Van Balkom, Beekman, De Beurs, Deeg, Van Dyck & Van Tilburg, 2000) Secondly, the quality of life is clearly affected in anxiety-ridden elderly people to a comparable level as observed in elderly adults suffering from major depression they experience significantly more decline in physical health, general well-being, and social and overall functioning compared to asymptomatic elderly (Wetherell et al , 2004a) Thirdly, although hardly effective in reducing anxiety symptoms, the LASA data showed a frequent and increasing (from 25% to 43% in six years) prescription of benzodiazepines in older adults with serious anxiety complaints (Van Balkom et al , 2000, De Beurs et al , 1999, Schuurmans et al , 2005) Finally, even though a multitude of confounding variables among which age, depression, somatic diseases, smoking and drinking, physical activity, and overweight were controlled for, a recent study showed that in men suffering from late-life anxiety disorders the risk of mortality had increased with 78% relative to asymptomatic controls (Van Hout, Beekman, De Beurs, Comijs, Van Marwijk, De Haan et al , 2004)

In summary, anxiety disorders are highly prevalent in later life, are characterized by a chronic course, and are associated with substantial physical and mental comorbidity, a decline in (social) functioning and hence a substantially reduced quality of life

1.6 The diagnosis of late-life anxiety disorders may be complicated by age-related variables

Given the high prevalence of late-life anxiety disorders it is remarkable as well as undesirable that so few sufferers are properly referred to and thus adequately treated by specialized mental health-care providers Apparently, primary care professionals have great difficulty recognizing the condition and are thus also unfamiliar with the available treatment options Several reasons underpin this assumption Most elderly people with anxiety problems tend to attribute their symptoms to physical causes (Gurian & Miner, 1991, Sheehan, Philpot & Banerjee, 2002) Moreover, the process of ageing is often associated with more physical illness and other (un)explained physical symptoms As

in the elderly symptoms of anxiety and depression often coincide with serious somatic conditions, especially cardiovascular involvement and chronic obstructive pulmonary diseases (COPD), separating anxiety disorders from 'normal' anxiety induced by medical problems and procedures may be difficult (Seung Kim, Braun & Kunik, 2002) As physicians will likely be targeting diagnostic procedures for the somatic symptoms, which may also cover specific physical anxiety symptomatology, the diagnosis of a comorbid anxiety disorder may easily be missed (Wetherell, Maser & Van Balkom, 2005a) This is illustrated by earlier findings after having been referred to a hospital under suspicion of a coronary artery disease and following negative cardiovascular screening, 40 to 60% of the elderly patients were diagnosed with a panic disorder (Katon, Hall, Russo, Cormier, Hollifield, Vitaliano, 1988, Wulsin, Hillard, Geier, Hissa & Rouan, 1988) If screened properly, an accompanying panic disorder may also often be diagnosed in COPD patients (Cassem, 1995, Karajgi, Rifkin, Doddi & Kolli, 1990) Additionally, the current generation of elderly may be less open in sharing psychological problems than the younger generations and may therefore have been struggling with anxiety symptoms for many years without ever receiving adequate treatment (Weijnen & De Beurs, 2001, Weijnen, Schuurman, Comijs, Emmelkamp, Van Dyck & Van Hout, 2006) A prospective cohort study showed that less than 5% of the elderly patients confronted with psychological problems consulted their GPs (Shah, McNiece & Majeed, 2001) The question whether they are reluctant in communicating their personal problems or whether they lack the necessary verbalizing skills to do so remains Also, the level of agreement between targeted screening for anxiety and depression in older patients and the diagnostic findings of GPs is low (Volkers, Nuyen, Verhaak & Schellevis, 2004, Watts, Bhutani, Stout, Ducker, Cleator, McGarry et al , 2002) Chronic somatic comorbidity and the absence of earlier mental problems also decreased the chance of a proper diagnosis (Nuyen, Volkers, Verhaak, Schellevis, Groenewegen & Van den Bos, 2005) Finally, it is plausible that ageing may lead to phenomenological differences with younger adults suffering from similar anxiety disorders and therefore possibly making an adequate diagnosis more difficult (Trimbos-instituut, 2008)

1.7 Phenomenological differences between older and younger adults suffering from anxiety

Several authors have stressed the necessity of differentiating between anxiety disorders in young and middle-aged individuals and older adults The main arguments are the supposed differences in phenomenology and outcome between the two age bands (Fuentes & Cox, 2000, Jeste, Blazer & First, 2005, Stanley & Beck, 2000) It may also be important to differentiate between an early and a late onset of the complaints in older

patients as age at onset may likewise have a differential impact on these parameters (Grant, Mancebo, Pinto, Williams, Eisen & Rasmussen, 2007; Sheikh, Swales, Carlson & Lindley, 2004a; Wetherell, Hopko, Diefenbach, Averill, Beck, Craske et al , 2005b). However, the criteria for the differentiation of early and late-onset anxiety seem fairly arbitrary and the threshold age range in previous studies varied from 30 to 60 years, with several retrospective and explorative studies using a threshold age of 55 to 60 years (Depp, Woodruff-Borden, Meeks, Gretarsdottir & de Kryger, 2005; Lenze, Mulsant, Mohlman, Shear, Dew, Schulz et al., 2005a; Le Roux, Gatz & Wetherell, 2005; Segui, Salvador-Carulla, Marquez, Garcia, Canet & Ortiz, 2000, Sheikh, King & Taylor, 1991). Other studies based their differentiation on epidemiological data (Katerndahl & Talamantes, 2000; Sheikh et al., 2004a). Unfortunately, a proper and valid definition of early- and late-onset anxiety disorders is as yet not available

Until now, differences in cognitive, emotional, and physical symptoms between younger and older adults with anxiety problems have mainly been studied in undiagnosed or outpatient populations with mixed symptoms. Taken together, the studies showed that in all three categories older adults reported less severe symptoms (Brenes, 2006; Crittendon & Hopko, 2006; Goldberg, Breckenridge & Sheikh, 2003; Hunt, Wisocki & Yanko, 2003; Klapow, Kroenke, Horton, Schmidt, Spitzer & Williams, 2002; Lau, Edelstein & Larkin, 2001). Other findings indicated that, in general, the experience of negative feelings and the intensity of emotional responses appeared to decrease with progressing age. This may possibly be attributable to a natural, age-related decrease in emotional responsiveness, i.e. a dampening of affective reactivity. Additionally, elderly people tend to be more in control of their emotional life and better able to cope with stressful life-events (Gross, Carstensen, Pasuphati, Tsai, Skorpen & Hsu, 1997; Jorm, 2000). So far, however, these factors have never been systematically examined and mentioned assumptions are hence not based on consistent findings. Moreover, most studies in this area suffered from methodological shortcomings (Jorm, 2000). Thus, fundamental research on these issues, also in relation to medical problems, psychiatric comorbidity (e.g. depression), and the nature of anxiety in elderly people, is still in its infancy (Bryant, Jackson & Ames, 2008).

Age-related differences in the phenomenology of late-life anxiety disorders have, so far, only been explicitly studied in patients diagnosed with PD(A). Furthermore, the phenomenology of panic attacks in younger and older adults have also been investigated in non-clinical populations and populations with mixed anxiety disorders. The following paragraph therefore focuses on these age-dependent phenomenological differences in confirmed PD(A) patients and individuals experiencing panic attacks that are not directly related to PD(A).

Empirical findings of age-related differences in cognitive, affective, behavioural, and physiological symptoms in panic disorder

Several studies demonstrated that, relative to the values obtained in younger individuals, ageing and onset at an older age is associated with a decrease in both cognitive and affective anxiety, as well as in physiological arousal. It is suggested that normal age-related psychophysiological changes and the later symptom onset are responsible for these differences, which would explain why PD(A) has been considered to be a less severe disorder later in life (Sheikh et al., 2004a). Next, the various findings are discussed in more detail.

In non-clinical individuals in a first study, the severity scores for panic attacks and phobic avoidance of the older adults were lower than those of their younger peers. When the onset of their panic attacks had occurred at an older age, their symptoms were even more reduced compared to those reported by their age peers whose symptoms had started at a younger age (Sheikh et al., 1991). A second study in a non-clinical cohort revealed a 43% decrease in the prevalence of panic attacks in the older adults compared to a 26% reduction in the younger participants. Additionally, after controlling for physical health, cognitive anxiety was found to be a stronger predictor of non-clinical panic attacks in the older adults than self-reported physiological symptoms, whereas in the younger adults the latter symptoms were more predictive. Cognitive anxiety was accordingly proposed as the more relevant phenomenon for the assessment of panic in elderly people (Depp et al., 2005). Using a carbon dioxide challenge in non-clinical subjects aged between 18 and 62 years, a third study (Griez, Colasanti, Van Diest, Salamon & Schruers, 2007) showed an age-related decline in the emotional anxiety response. Although in older adults a decline in the physiological arousal of anxiety is also plausible, empirical studies in this particular age group are scarce and often hampered by methodological limitations (Lau et al., 2001). In this context, the study of Flint and colleagues (1998) warrants mentioning. They found the responsiveness of cholecystokinin-4 (CCK-4) to be challenged in both younger (20-35 years) and older non-clinical adults (65-plus years), but also observed a waning of panic symptoms and physiological arousal in the older participants. These non-clinical findings may support the widely held clinical view that anxiety and panic symptoms decline in later life. Age-related empirical findings in clinical populations with PD(A) are scarce. Katerndahl and Talamantes (2000) confirmed the notion that an onset of panic attacks in later life is associated with less symptomatology and less psychiatric morbidity. However, their findings were limited by their cross-sectional design and the mixed psychiatric morbidity of their study sample. Only two research reports are available that specifically evaluated age-related differences in PD(A) phenomenology. Segui and colleagues (2000) recorded less frequent and less severe panic symptoms and lower scores on both observer-rated and self-report scales for their older respondents who had a PDA onset after age 60 than they did for the respondents with an onset at a

younger age However, phobic avoidance, a core symptom of PDA, did not differ in the two age groups Sheikh and colleagues (2004) later partially confirmed these findings compared to the younger respondents, their 60-plus PD patients reported less severe physical, affective, and cognitive anxiety symptoms They further divided their over-60s group into an early- and a late-onset subgroup, setting the age at onset of the latter subgroup at 35-plus years in accordance with the available epidemiological findings Although compared to the early-onset group the self-reported physical symptoms were lower in the late-onset patients, no such onset-related differences were found for subjective PD severity or the scores for affective and cognitive anxiety These findings seem to underpin a declining severity of symptoms in later life However, the report suffered from a major limitation, viz the absence of phobic avoidance scores, rendering the evidence somewhat inconclusive and not applicable to older adults suffering from PDA

In sum, anxiety disorders remain among the most common psychiatric syndromes in older adults substantially reducing their quality of life However, most elderly patients suffering from serious anxiety remain undiagnosed and therefore untreated, which may partially account for the scarcity in empirical research into the management of late-life anxiety and panic disorder in particular

Next, barriers in the research into the treatment of late-life anxiety disorders are summarized, followed by an overview of the available empirical findings

1.8 Older age does not hinder adequate management of anxiety disorders

Until now, the recruitment and inclusion of a sufficient number of eligible patients proved a major obstacle to clinical trials evaluating the treatment of late-life anxiety disorders (see e g Cassidy, Baird & Sheikh, 2001 and Wetherell & Gatz, 2001) This lack of participants first and perhaps foremost arises from the problem of underdiagnosing and undertreatment, as well as an inability or reluctance in elderly patients to seek help for their anxiety complaints Also problems with transportation (in terms of options, time and costs) to and from outpatient clinics and research facilities, comorbid somatic diseases, as well as polypharmacy in the elderly (of prescribed and over-the-counter medication) contribute to the scarcity of RCTs in this field (Cassidy et al , 2001) As decreasing the age for inclusion is a viable strategy to recruit more participants (Macias, Ramsey & Rowan, 2007), many RCTs into late-life anxiety disorders included patients as 'young' as 55 or 60 years Although thus preventing problems in recruitment, most studies did not adequately differentiate between age bands, say respondents of 55-75

years and those over 75 years, despite the substantial variability in physical and mental health status and scale of societal activities. Accordingly, differences in recruitment strategies and the variability in ageing effects have limited the generalizability of the findings from the RCTs conducted so far (Izal, Nuevo, Montorio & Perez-Rojo, 2007).

However, there has been extensive research into the management of anxiety disorders in populations aged between 18 and 65 years, as is reflected in several systematic and meta-analytic reviews, which has led to international and national guidelines stipulating CBT and antidepressants as the two treatments of choice[3]. In addition, the few findings from RCTs focusing exclusively on elderly patients (60-plus and 65-plus) also tentatively indicated that both regimens may also be the optimal treatments for the management of late-life anxiety disorders (Hendriks, Oude Voshaar, Keijsers, Hoogduin & Van Balkom, 2008a; Pinquart & Duberstein, 2007). These early findings thus support the multidisciplinary guidelines the National Institute for Mental Health (Trimbos-instituut) had also adopted for the treatment of anxiety disorders in the elderly (http://www.ggzrichtlijnen.nl/ 'Addendum ouderen'). In the next two sections the empirical findings for the psychological and the pharmacological treatment of anxiety disorders are described separately.

Psychological treatment

Although anxiety disorders are highly prevalent in later life causing a serious decline in quality of life, many health professionals and researchers seem to entertain a persistent but unexpressed idea that targeted psychological treatment is unsuited in the elderly. Prompted by this therapeutic nihilism studies into the psychological treatment of late-life anxiety disorders were initiated during the 1990s. The main objective was to prove that well-established manualized CBT for the treatment of anxiety disorders was also effective in older populations, i.e. in patients over the age of 60 years. Although it was believed that the CBT programme should be adapted to the specific needs of the elderly and should be offered in a group format (Stanley & Averill, 1999; Stanley & Beck, 2000), there is no or very little actual evidence for these assumptions. Two trials did study age-specific adaptations in manualized CBT for generalized anxiety disorder (GAD) in older adults (Mohlman, Gorenstein, Kleber, de Jesus, Gorman & Papp, 2003; Stanley, Beck, Novy, Averill, Swann, Diefenbach et al., 2003a). The adaptations in essence referred to a distinct focus on education, a frequent use of reminders and repetition of the treatment rationale, offering frequent help with the homework assignments, and the exploitation of adherence enhancement strategies. In the Mohlman study the adapted CBT showed on more outcome measures improvement compared to the standard CBT and in the Stanley

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study participants in the adapted CBT responded more compared to a minimal contact control condition However, as both trials were small and the adapted protocolized CBT was not directly compared to standard CBT, it is premature to conclude that age-specific adaptations indeed enhance the efficacy of CBT To date, there is no systematic research that has investigated which adaptations are needed to improve the effects of CBT for late-life anxiety disorders nor studies that determined the extent to which modifications improve efficacy

The results of RCTs into the effectiveness of protocolized CBTs for late-life anxiety disorders reported so far are promising However, evidence is predominantly limited to GAD or mixed anxiety disorders Until now, six RCTs showed evidence of CBT effectiveness in older adults suffering from GAD (Mohlman et al , 2003, Stanley et al , 2003a, Stanley, Hopko, Diefenbach, Bourland, Rodriguez & Wagener, 2003b, Stanley, Beck & De Witt Glasco, 1996, Wetherell, Gatz & Craske, 2003) In the studies CBT consisted of progressive muscle relaxation training, cognitive restructuring, worry exposure, and worry behaviour prevention according to manuals specifically developed for the management of GAD (Borkovec & Costello, 1993, Craske, Barlow & O'Leary, 1992) Outcome measures showed large effect sizes for worry, anxiety, and depression, both at post-treatment and at follow-up, and CBT showed unequivocal effects relative to waiting-list control conditions Four trials compared CBT with an active control condition consisting of other psychological treatments such as supportive counselling or a discussion group (Stanley et al , 1996, Stanley et al , 2003a, Stanley et al , 2003b, Wetherell et al , 2003), but here superiority of CBT was not unambiguous (Stanley et al , 1996, Wetherell et al , 2003)

In two other RCTs the effectiveness of CBT was confirmed in elderly populations with mixed anxiety disorders (Barrowclough, King, Colville, Russell, Burns & Tarrier, 2001, Schuurmans, Comijs, Emmelkamp, Gundy, Weijnen, Van den Hout et al , 2006) In both studies PD and GAD were the two most frequent disorders (70% or more) and CBT was conducted in accordance with evidence-based manuals (Borkovec & Costello, 1993, Clarke et al , 1993, Wells, 1997) With large post-treatment and follow-up effect sizes (up to 12-months) for anxiety and depression, Barrowclough and colleagues (2001) demonstrated the superiority of CBT in comparison to supportive counselling Schuurmans and colleagues (2006) compared CBT to sertraline and found both post-treatment and follow-up (3-month and 1-year) effects to show sertraline superior to CBT, with large effect sizes for anxiety and depression

Although promising, some critical remarks have to be made in connection with the reported results Most of the mentioned CBT studies of elderly patients (Barrowclough et al , 2001, Schuurmans et al , 2006, Stanley et al , 2003, Wetherell et al , 2003) were

hampered by recruitment difficulties and high attrition rates (in excess of 25%) and concerned community-dwelling, relatively younger and relatively healthy participants. And, as mentioned above, the greater majority of the published RCTs into the psychological treatment of late-life anxiety disorders focused on populations diagnosed with GAD or mixed anxiety disorders, leaving most other anxiety syndromes underinvestigated and thus preventing generalization of the results to 'older' (e.g. 75-plus) elderly patients and populations suffering from specific anxiety disorders.

Pharmacological treatment

In stark contrast to the volume of RCTs testing pharmacological agents for major depression in later life, psychopharmacological interventions for late-life anxiety disorders have hardly been systematically studied (Mottram, Wilson & Strobl, 2006; Pinquart, Duberstein & Lyness, 2006). The data on late-life depression showed SSRIs and TCAs to be comparably effective. Although the tolerability of both groups of agents was satisfactory, the classical TCAs (e.g. amitriptyline and clomipramine) were associated with significantly more side effects and dropout than the SSRIs (24% vs. 18%; Mottram et al., 2006; Wilson & Mottram, 2004). As to the pharmacological treatment of late-life anxiety disorders, Pinquart and Duberstein (2007) conducted a meta-analytic review of all available naturalistic studies and RCTs. With 0.81 and 1.76, respectively, the pre-post effect sizes for CBT and pharmacological treatment were large. The effect sizes for benzodiazepines (1.76) and SSRIs (1.68) were comparable, while they were 1.14 for TCAs. Based on these data, pharmacological treatment was recommended as the treatment of choice for late-life anxiety. The findings warrant a more balanced interpretation, however. Although all 23 reviewed studies tested pharmacological treatments, only four were RCTs evaluating specific late-life anxiety disorders. One of these showed venlafaxine to be superior to placebo in the treatment of late-life GAD (Katz, Reynolds III, Alexopoulos & Hackett, 2002), while two reported large effect sizes for SSRIs in the management of mixed anxiety disorders (Lenze, Mulsant, Shear, Dew, Miller, Pollock et al., 2005b; Schuurmans et al., 2006) with the distinction that in these latter two trials over 70% of the patients were diagnosed with GAD. And lastly, in the fourth study both alprazolam and imipramine showed large effect sizes compared to placebo in the treatment of late-life PD. This was however a small-scale pilot study (Sheikh & Swales, 1999). With a total number of 324 participants and cohorts ranging from 25 to 184 patients, the majority of these four RCTs were too small-scale to found the recommendations on.

In contrast to guidelines 25% of all elderly patients are prescribed benzodiazepines, i.e. six times more often than antidepressants, as first-line agents in the management of late-life anxiety disorders (De Beurs et al., 1999). Six years later in the same population, this percentage was increased to 43%, which was still three times more often than antidepressants (Schuurmans et al., 2005). Frequent use of prescription benzodiazepines

is, however, associated with serious drug-related hazards such as an increased risk of falls and fractures and possible aggravation of cognitive difficulties (Paterniti, Dufouil & Alperovitch, 2002; Wang, Bohn, Glynn, Mogun & Avorn, 2001a; Wang, Bohn, Glynn, Mogun & Avorn, 2001b). But what are the underlying reasons for prescribing benzodiazepines, then? First of all, the agents are highly effective in the management of late-life anxiety (Pinquart & Duberstein, 2007). Furthermore, many older adults resist the use of antidepressants based on a fear of dependence, prior negative experiences, a resistance to viewing their symptoms as a medical illness, and concern that antidepressants will prevent natural feelings (Givens, Datto, Ruckdeschel, Knott, Zubritsky, Oslin et al., 2006). Moreover, especially in older adults the use of both SSRIs and TCAs is not without risk. The high prevalence of somatic syndromes such as cardiovascular diseases and arthrosis, and the subsequent use of medications in this population increase the risk of interaction with SSRIs. The concurrent use of SSRIs and aspirin or NSAIDs, for example, raises the risk of gastrointestinal bleeding (Weinrieb, Auraicombe, Lynch & Lewis, 2005, Yuan, Tsoi & Hunt, 2006). Furthermore, previous findings showed that in elderly patients using either benzodiazepines or antidepressants the risk of falls and fractures was comparable, even for the preferred SSRIs (Ensrud, Blackwell, Mangione, Bowman, Whooley, Bauer et al., 2002; Ensrud, Blackwell, Mangione, Bowman, Bauer, Schwartz et al., 2003; Hartikainen, Lonnroos & Louhivuori, 2007; Liu, Anderson, Mittmann, To, Axcell & Shear, 1998).

In conclusion, research into the available psychopharmacological approaches to anxiety disorders to date indicates that the tolerability and effectiveness of antidepressants is comparable in younger and elderly adults. However, the benefits should be weighed carefully against the preferences of the elderly patients themselves, the relative risks of antidepressants, the severity of the anxiety symptoms as well as the available alternative, behavioural approaches like CBT.

1.9 Aims and outline of this thesis

Prompted by all the conflicting evidence and the considerable gaps in our knowledge, the work presented in this thesis was aimed at expanding the empirical data concerning the efficacy of antidepressants and CBT in older adults, that is, patients over 60 years of age that have been diagnosed with anxiety disorders in general, and finding the first empirical evidence for elderly patients with confirmed PD(A). Although RCTs and meta-analyses have amply confirmed the effectiveness of both treatments in younger adults, RCTs directly comparing the two approaches in elderly patients suffering from anxiety in general are scarce, and, trials evaluating late-life PD(A) are absent, leaving the question whether CBT is to be preferred over specific pharmacological or other psychological

treatments unanswered. In the case of PD(A), it has never been tested whether the guideline-recommended treatments with antidepressants or CBT are effective or even feasible in elderly populations. Accordingly, the main research questions posed were:

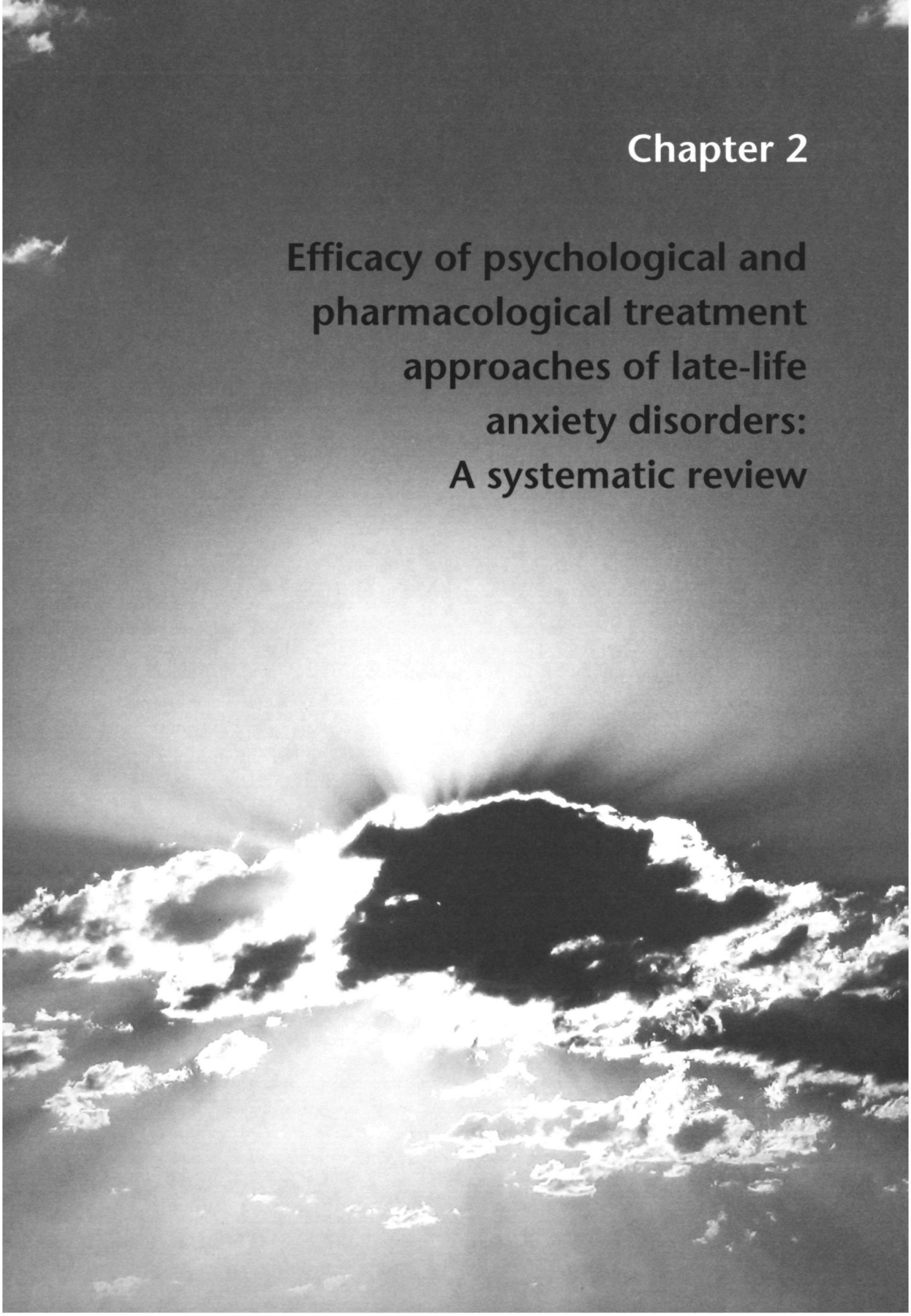
1. Are both CBT and antidepressants efficacious in the treatment of late-life anxiety disorders?
2. Is CBT more effective than an active control comparison in the treatment of late-life anxiety disorders?
3. Are both paroxetine and CBT effective and well-tolerated treatments for PD(A) in older adults?
4. Does the content of agoraphobic cognitions differ between younger and older adults suffering from PDA?
5. Is CBT as effective and as well-tolerated in older adults diagnosed with PDA as it has been found to be in younger adults?
6. Are age, age at onset and duration of illness related to outcome in CBT for PDA?
7. Are age and duration of illness related to paroxetine and CBT outcome in late-life PDA?

First, in Chapter 2 the available RCTs of treatment approaches for late-life anxiety disorders are systematically reviewed, after which in Chapter 3 a meta-analysis is made of the efficacy of CBT in particular.

Chapter 4 subsequently describes an RCT comparing the effects of paroxetine and CBT to a waiting-list control in the treatment of late-life PD(A) and in Chapter 5 the content of agoraphobic cognitions is compared between younger and older adults with PDA. Chapter 6 comprises a direct comparison of the effects and tolerability of CBT in a cohort of older and a cohort of younger adults diagnosed with PDA.

In Chapter 7 is investigated whether and to what extent age, age of onset, and duration of illness predict the outcome of CBT for PDA in both younger and older adults, while Chapter 8 explores possible differential effects of age and duration of illness on predicting outcome following treatment with paroxetine or CBT in elderly patients with PD(A).

Finally, in Chapter 9 the overall results of the studies reported are summarized and put into context.



Chapter 2

Efficacy of psychological and pharmacological treatment approaches of late-life anxiety disorders: A systematic review

This chapter has been submitted for publication:

Hendriks, G.J., Keijsers, G.P.J., Verbraak, M.J.P.M. & Hoogduin, C.A.L. Efficacy of psychological and pharmacological treatment approaches of late-life anxiety disorders: A systematic review

2.1 Introduction

With prevalence rates up to 10 to 15% (Beekman et al., 1998; Flint, 1994) anxiety disorders can be said to be widespread in later life. The Longitudinal Aging Study Amsterdam (LASA) reported generalized anxiety disorders (GAD) and phobias as the most common, with a 6-month prevalence of 7.3% and 3.1%, respectively, and considerably lower rates for panic and obsessive-compulsive disorders (1.0% and 0.6%, respectively; Beekman et al., 1998). And yet, although the number of reports on late-life anxiety disorders has risen since the end of the previous millennium, research on this topic is still scarce when compared to the volume of studies on other common mental disorders manifesting themselves at older age. Several biases lie at the root of this lack in scientific attention. Late-life anxiety is generally viewed as a minor health problem not warranting specific treatment. Recent findings, however, show that, if left untreated, late-life anxiety has a tendency to become chronic and is associated with a substantial risk of major depression, increases in health-care consumption, reduced quality of life, more disability, and increased relative mortality risk (Beekman et al., 2000; Brenes, Kritchevesky, Mehta, Yaffe, Simonsick, Ayonayon et al., 2007; De Beurs et al., 1999; Schuurmans et al., 2005, Van Hout et al., 2004; Wetherell et al., 2004a; Wetherell et al., 2005a). Nevertheless, despite the high prevalence of anxiety disorders and the substantial health loss, the majority of elderly people suffering from the symptoms does not receive appropriate treatment: only 5.1% is offered psychological treatment and 3.8% is prescribed an antidepressant. In contrast, benzodiazepine consumption is as high as 25-43% (De Beurs et al , 1999; Schuurmans et al., 2005). The undertreatment of late-life anxiety disorders is, among other causes, explained by the fact that few older adults are being referred for targeted treatment: the referral rate from primary care to a mental-health specialist (17%) is three times lower than it is for late-life depression (55%, Ettner & Hermann, 1997). This would also explain the low number of randomized controlled clinical trials (RCTs) for late-life anxiety.

In the guidelines (e.g. APA, 2002) cognitive-behavioural therapy (CBT) and antidepressants are recommended as evidence-based treatments for anxiety disorders in the general, middle-aged population. Recent meta-analyses of psychological and pharmacological treatments of anxiety in older adults, however, included both studies on anxiety symptoms and anxiety disorders and in their analyses the authors did not differentiate between type of psychological intervention (Nordhus & Pallesen, 2003, Pinquart & Duberstein, 2007). The positive results of CBT and antidepressants for anxiety disorders in the general population prompted the present overview of all controlled clinical trials of psychological treatments and antidepressants that have been conducted thus far in elderly patients suffering from anxiety disorders.

2.2 Method

We based our review on a literature search of the databases of *PubMed and PsycINFO*, and the *Cochrane Central Register of Controlled Trials* for the period 1977 through July 2007 using the keywords *late-life, elderly, aged* or *old age* combined with the keywords *anxiety, anxiety disorder, panic disorder, obsessive(-)compulsive disorder, generaliz(s)ed anxiety disorder, social anxiety disorder, social phobia, post(-)traumatic stress disorder, specific phobia* and the keywords *therapy, psychotherapy, treatment, psychological treatment, cognitive treatment, behavio(u)r(al) treatment, pharmacotherapy* and *medical treatment*. We subsequently manually inspected the reference lists for any additional RCTs evaluating pharmacotherapeutic and psychological treatments for late-life anxiety disorders.

Inclusion criteria

The first and third author (G.J.H. and M.J.P.M.V.) independently checked all inclusion and exclusion criteria for all identified studies. To be included in the review studies needed to meet the following criteria:

a A diagnosis of anxiety disorder according to ICD-10, DSM-III, DSM-III-R, or DSM-IV as verified by a (semi-)structured clinical interview;
b The use of valid outcome measures (self-report questionnaires or clinical interviews);
c Pre- and post-treatment results presented for each treatment condition;
d A mean or median age of 60 years and older; and
e A randomized controlled research design.

Selection procedure, data extraction and quality assessment

The coding form listed the following items: year of publication, diagnosis, diagnostic criteria, duration of the disorder, age and sex of the patients, type and duration of the treatment, presence and duration of the follow-up assessment(s), outcome measures and the results on the post-treatment outcome measures and finally type of control condition. Type of control condition was classified as either a waiting-list (WL) or an active control condition. The active control condition was defined as either treatment as usual (TAU) or any other treatment strategies that provided a contact frequency comparable to the ones in the CBT, the pharmacotherapy or placebo condition.

To obtain a single, jointly approved coding per article, between-rater differences in the separate coding forms were discussed and resolved by consensus or by referring to the data in the original article.

Both authors also independently assessed the methodological quality of the included studies using the Amsterdam-Maastricht consensus list, ranging from 0 [poor quality] to 19 [excellent quality] (Van Tulder, Assendelft, Koes & Bouter, 1997). The Amsterdam-

Maastricht consensus list has previously been used in meta-analytic reviews of RCTs of psychiatric disorders (Van Boeijen, Van Balkom, Van Oppen, Blankenstein, Cherpanath & Van Dyck, 2005; Oude Voshaar, Couvee, Van Balkom, Mulder & Zitman, 2006) and covers the Chalmers criteria usually applied in the assessment of study quality (Chalmers, Smith, Blackburn, Silverman, Schroeder, Reitman et al., 1981).

Outcome analysis

In our evaluation severity of anxiety represented the primary outcome measure and depressive symptoms a secondary outcome measure. The most frequently used outcome assessment methods in the effect studies of psychological interventions were the Beck Anxiety Inventory (Beck, Epstein, Brown & Steer, 1988), the Penn State Worry Questionnaire (Meyer, Miller, Metzger & Borkovec, 1990), the State-Trait Anxiety Inventory (Spielberger, 1983), the Hamilton Anxiety Rating Scale (Hamilton, 1959) and the Beck Depression Inventory (Beck, 1988). In the pharmacological studies the outcome assessments comprised the Hamilton Anxiety Rating Scale (Hamilton, 1959) and the Hamilton Depression Rating Scale (Hamilton, 1960). We computed treatment effect sizes (ES) within and between groups using Cohen's *d* (Cohen, 1988) of all primary and secondary outcome measures for all reported post-treatment and, if available, follow-up measures separately. Effect sizes were calculated as the difference between means divided by the pooled standard deviations of the means (Cohen, 1988). A composite ES for anxiety was computed by calculating the mean effect size for the outcome measures on severity of anxiety. The same procedure was used for computing a composite ES for depression.

2.3 Results

Search strategy

We identified 56 titles as potentially relevant to the treatment of late-life anxiety disorders. Based on systematic screening we excluded 46 papers because they did not use a randomized controlled design or did not meet the diagnostic criteria of a specific anxiety disorder. Ultimately, the following 10 papers describing 12 studies met the full inclusion criteria of the current study: Barrowclough et al., 2001; Gorenstein, Kleber, Mohlman, De Jesus, Gorman & Papp, 2005; Lenze et al., 2005b; Mohlman et al., 2003; Schuurmans et al., 2006; Sheikh & Swales, 1999; Stanley et al., 1996; Stanley et al., 2003a; Stanley et al., 2003b; and Wetherell et al., 2003. Although our search was directed at all ICD- and DSM-specified anxiety disorders, our selection procedure only yielded references for RCTs on GAD, panic disorder, or mixed populations with predominantly GAD and panic disorder.

Study quality

Table 2-1 lists the sum scores of the Amsterdam-Maastricht consensus list (range 0-19) for all 10 studies indicating their study quality. Since in psychotherapy studies blinding to the treatment condition for patients as well as for therapists is difficult and is rarely realized, the expected maximum score is 17. Scores ranged from 12 to 17 (M = 14.0; SD = 1.6), reflecting a moderate to good study quality with few between-study differences (Van Tulder et al., 1997).

Study characteristics and effect sizes

In Table 2-2 the study characteristics are summarized per study retrieved. The selected studies included a total of 470 patients with a range of 12 to 84 patients per study. Mean ages varied from 61.3 to 72.0 years and 72.7% were women Five studies (Mohlman et al., 2003; Stanley et al., 1996; Stanley et al., 2003a; Stanley et al., 2003b; Wetherell et al., 2003) exclusively included patients with a primary diagnosis of GAD. Four studies (Barrowclough et al., 2001; Gorenstein et al., 2005; Lenze et al., 2005; Schuurmans et al., 2006) examined a mixed population or various anxiety disorders with panic disorder, with GAD being the most frequent (> 70%). Comorbidity with depression (major depression or dysthymia) or another anxiety disorder was common and varied per study from 9.5% to 68% (mean: 46%). The mean dropout percentage was 26.4% (range: 0%-41.2%; see Table 2-2). The active treatment phases ranged from 8 to 15 weeks. In the pharmacotherapy conditions medication was not tapered off. Eight studies reported follow-up data with follow-up intervals varying from 3 to 12 months. CBT was compared with medical treatment and WL (Schuurmans et al., 2006), with TAU (Stanley et al., 2003a; Stanley et al., 2003b), with a WL condition (Mohlman et al., 2003; Schuurmans et al. 2006; Wetherell et al., 2003), with supportive psychotherapy (SUP; Barrowclough et al., 2001; Stanley et al., 1996) or with a discussion group (DG; Wetherell et al., 2003). The pharmacological treatments (Lenze et al., 2005b; Schuurmans et al., 2006, Sheikh & Swales, 1999) were compared with a WL condition and CBT (Schuurmans et al., 2006) or placebo (Lenze et al., 2005b; Sheikh & Swales, 1999).

For anxiety the post-treatment CBT ES ranged from 0.4 to 2.0 and at follow-up from 0.4 to 1.8. Pharmacotherapy was also effective with post-treatment ES ranging from 0.8 to 1.5, with the one study that also presented follow-up data reporting an effect size of 1.1 after 12 months (Schuurmans et al., 2006). Three CBT studies (Stanley et al., 1996; Barrowclough et al., 2001; Wetherell et al., 2003) included SUP or DG as the active control treatment and the post-treatment ES on anxiety for the two conditions ranged from 0.5 to 0.9 and at follow-up from 0.5 to 1.0. With a range of -0.3 to 0.4 the ES for the WL control condition and TAU were small or even negative. For depression the post-treatment and follow-up ES for CBT and pharmacotherapy were equally large (Table 2-2).

Table 2-1. Validity scores for all included studies as based on the Amsterdam-Maastricht consensus list

Study	Stanley et al. (1996)	Barrow-clough et al. (2001)	Mohlman et al. (2003)	Stanley et al. (2003a)	Stanley et al. (2003b)	Wetherell et al. (2003)	Gorenstein et al. (2005)	Schuurmans et al. (2006)	Sheikh & Swales (1999)	Lenze et al. (2005b)
Validity criteria										
Adequate randomization procedure	+	+	+	+	+	+	+	-	+	+
Concealed random allocation of treatments	-	+	-	-	-	-	-	+	-	+
Baseline similarity tested	+	+	+	+	+	+	+	+	+	+
Control for co-interventions in design	-	-	+	+	+	+	+	+	-	+
Check for adherence to interventions	+	+	+	-	+	+	+	-	-	-
Valid outcome measures	+	+	+	+	+	+	+	+	+	+
Relevant outcome measures	+	+	+	+	+	+	+	+	+	+
Outcome assessor blinded	0	+	+	-	+	+	+	-	-	+
Therapist blinded	0	-	0	-	0	0	0	0	+	+
Patient blinded	0	-	0	-	0	0	0	0	+	+
Withdrawals and dropouts (proportion; inequality between groups; reasons for withdrawal/dropout reported)	+	+	+	+	+	+	+	+	-	+
Identical timing of outcome assessment for all intervention groups	+	+	+	+	+	+	+	+	+	+
Intent-to-treat analyses	-	-	-	-	+	+	+	+	-	+
Descriptive criteria										
Specification of eligibility criteria	+	+	+	+	+	+	+	+	+	+
Description of interventions	+	+	+	+	+	+	+	+	+	+
Follow-up	+	+	+	-	+	+	+	+	-	-
Adverse event	0	0	0	+	0	0	0	+	+	+
Statistical criteria										
Sample size: to be presented at randomization and outcome	+	+	+	+	+	+	+	+	+	+
Presentations of point estimates and distribution measures	+	+	+	+	+	+	+	+	+	+
Total score (range 0-19)	12	14	14	12	15	15	15	14	12	17

Table 2-2. Overview of all randomized controlled trials on late-life anxiety disorders (Cohen's *d* for pre-post

	N	Age (*SD*)	Anxiety disorder	Co-morbidity	Comparison	Treatment
Stanley et al. (1996)	46	68.3 (6.6)	GAD	48%	CBT SUP	14 weekly group sessions
Barrowclough et al. (2001)	46	72 (6.2)	Panic disorder with/without agoraphobia, social phobia, GAD, anxiety disorder n.o.s.	23%	CBT SUP	8-12 weekly individual sessions
Mohlman et al (2003)	42	67 1 (5.3) 65.7 (4.7) 68.5 (11.4) 66.9 (9.8)	GAD	58%	CBT WL CBT+ WL	13 weekly individual sessions and 6 monthly FU-sessions Idem, but modified
Stanley et al. (2003b)	12	70.6 (5.6)	GAD	48%	CBT + TAU	8 weekly individual sessions
Stanley et al (2003a)	80	80 (5.0)	GAD	65%	CBT MCC	15 group sessions
Wetherell et al. (2003)	75	67.1 (8.2)	GAD	52%	CBT DG WL	12 group sessions 12 group sessions
Gorenstein et al. (2005)	42	67.8 (7.1) 68.7 (6.6)	GAD, panic disorder with/ without agoraphobia, anxiety disorder n.o.s.	9.5%	CBT+MM MM	13 weekly individual sessions and medical consultation Medical consultation
Schuurmans et al. (2006)	84	70.7 (6.6) 69.8 (5.5) 66.9 (6.0)	GAD, panic disorder with/ without agoraphobia, social phobia	20% depression; 43% anxiety disorder	CBT SER WL	15 weekly individual sessions 8 medical consultations (15 weeks)
Sheikh & Swales (1999)	25	61.3 (5.4) 62.8 (5.6) 59.3 (5.1)	Panic disorder with/without agoraphobia	68%	IMI ALP PLAC	8 weeks 8 weeks 8 weeks
Lenze et al. (2005b)	34	70.7 (6.8) 68.1 (3.9)	GAD, panic disorder with/ without agoraphobia, PTSD	62%	CIT PLAC	8 weeks

ALP = alprazolam, CIT = citalopram, DG = discussion group; FU = follow-up, GAD = generalized anxiety disorder, IMI = imipramine, MCC = minimal contact control; MM = medical management, n.o.s = not otherwise specified, PLAC = placebo, PT = post-treatment; PTSD = posttraumatic stress disorder; SER = sertraline, SUP = supportive psychotherapy, TAU = treatment as usual; WL = waiting list.

treatment effect size)

Cohen's *d* for anxiety			Cohen's *d* for depression			Drop-out	Antidepressants/
PT	FU3/6	FU 12	PT	FU 3/6	FU 12		benzodiazepines
0.9	1.2		1.1	1.2		30.8%	Wash-out
0.9	1 0		1.1	1.0		35.0%	
1.4	1.6/1.7	1.8	1.3	1.2/1.6	1.5	29.6%	100%
0.7	0.5/0.9	0.8	0.6	0.4/0.6	0.6	14.3%	
0.7	0.6		0.6	1.6		23.1%	Wash-out
0.4			0.9			21.4%	
1 2	1.7		1.4	1.7		0%	
-0.1			0.6			0%	
2.0			1.0			16.6%	50%
-0.3			-0.5			8.4%	
0 9	1.1/1.1	1.3	1 2	1.1/0.9	1.4	25 6%	Wash-out
0.1			0.2			9.8%	
0.9	1.1		0.5	0.8		30.8%	29% daily, 11% > 2 times a week
0.5	0.6		0.4	0.7		30.8%	
0.1			0.1			8.7%	
1.0			1 1			39.1%	100% (because of study-design)
0.2			0.1			26.3%	
0.5	0.4	0.4	0.3	0.3	0.2	28.6%	Fixed dosage for benzodiazepines
1.0	1.1	1.1	0.9	0.9	0.8	37.9%	
0.0			0.0			30.8%	
1 5			1 4			0%	Wash-out
1.4			1.6			10.0%	
						85.7%	
1.8						17.6%	Fixed dosage for benzodiaz. (47%
1.0						11,7%	in CIT and 24% in PLAC)

The between-group post-treatment (and follow-up ES) for the anxiety measures revealed an advantage of CBT over SUP, DG, TAU and Minimal Contact Control (MCC; range 0.3 – 0.8), but not for CBT versus sertraline (ES = -0.06 – -0.12; Schuurmans et al., 2006) and for CBT versus SUP at follow-up in one comparison (ES = 0.1; Stanley et al. 1996). In most CBT versus active control comparisons the between-group ES for depression varied between 0.2 and 0.9, except in the Gorenstein et al. (2005) and Schuurmans et al. (2006) studies whose ES varied between -0 11 and 0.21. An ES difference of 0.2 or more in between-group comparisons for active controls is considered as clinically significant (Yon & Scogin, 2007).

2.4 Discussion

Main findings

With large effect sizes (> 0 8) in 9 of the 10 studies testing CBT and pharmacotherapy of late-life anxiety disorders relative to a waiting list or treatment as usual (TAU), our review found convincing evidence of superior treatment effects for CBT and medical interventions. The effect sizes for CBT were generally also larger than those for supportive psychotherapy or discussion groups, especially at follow-up. Interestingly, for anxiety CBT efficacy at follow-up had even improved in 7 of the 8 CBT studies. Moreover, CBT showed a superior effect on accompanying depressive symptoms. It is important to keep in mind that whereas pharmacotherapy was continued during follow-up in all studies, CBT was not

Of the three studies that had tailored their CBT programme to their elderly target group (Mohlman et al., 2003; Stanley et al., 2003a; Stanley et al., 2003b), two showed that the adaptations had improved the efficacy of the treatment compared with non-tailored CBT. However, the comprehensive and methodologically more sophisticated study by Stanley et al. (2003a) failed to find similar positive results.

Remarkably, one trial, i.e. the Schuurmans et al. study (2006), reported small CBT effect sizes that contrasted with all other studies we reviewed. Although Schuurmans and colleagues studied a mixed population, and thus had adopted less specific outcome measures, this was also the case in the Barrowclough et al. study (2001), which did show large effect sizes We discerned two differences in the two studies that might contribute to the lack of efficacy in the Schuurmans study Firstly, in the Barrowclough study the therapy sessions were audiotaped, which may have contributed to a strong protocol adherence, whereas in the Schuurmans study treatment adherence was monitored by means of the less accurate method of supervision meetings. Secondly, the therapists in the Schuurmans study reported problems with motivating their patients for the homework assignments, an essential element of CBT. No motivation problems were mentioned in the Barrowclough study.

Methodological considerations

The main limitations of the current review are inherent to the limited number of relevant studies, their relatively small sample sizes and high attrition rates, all preventing a thorough quantitative analysis. Moreover, as most studies exclusively examined patients with generalized anxiety disorders (GAD), the reported results can be generalized to this population only.

Given the average age of the elderly in Western-Europe and the USA, which is about 78 years, another critical point is the relatively low average age range of the participants in the reviewed studies, i.e. 61 to 72 years. Treatment outcome data for the oldest old are simply not available. In fact, we do not know if the efficacy rates we found in this review would be maintained in the very old with the same approaches, especially in view of any increased somatic comorbidity.

A recently published review on evidence-based psychological treatments of late-life anxiety analyzed 17 studies (Ayers, Sorrell, Thorp & Wetherell, 2007) and concluded, as we did in the present review, that the support for efficacy was strongest for CBT, and, to a lesser extent, for SUP and cognitive therapy. However, Ayers and team used less stringent inclusion criteria for diagnostic procedures, also included studies on subclinical anxiety symptoms in later life and failed to report dropout rates and within- and between-group effect sizes.

Although more thorough, with our review we failed to find conclusive proof for the efficacy of psychological and pharmacological interventions in anxiety disorders in later life. We nevertheless feel that the conclusions we have drawn bear sufficient relevance to both future research and the clinical practice considering that GAD is the most prevalent anxiety disorder in later life.

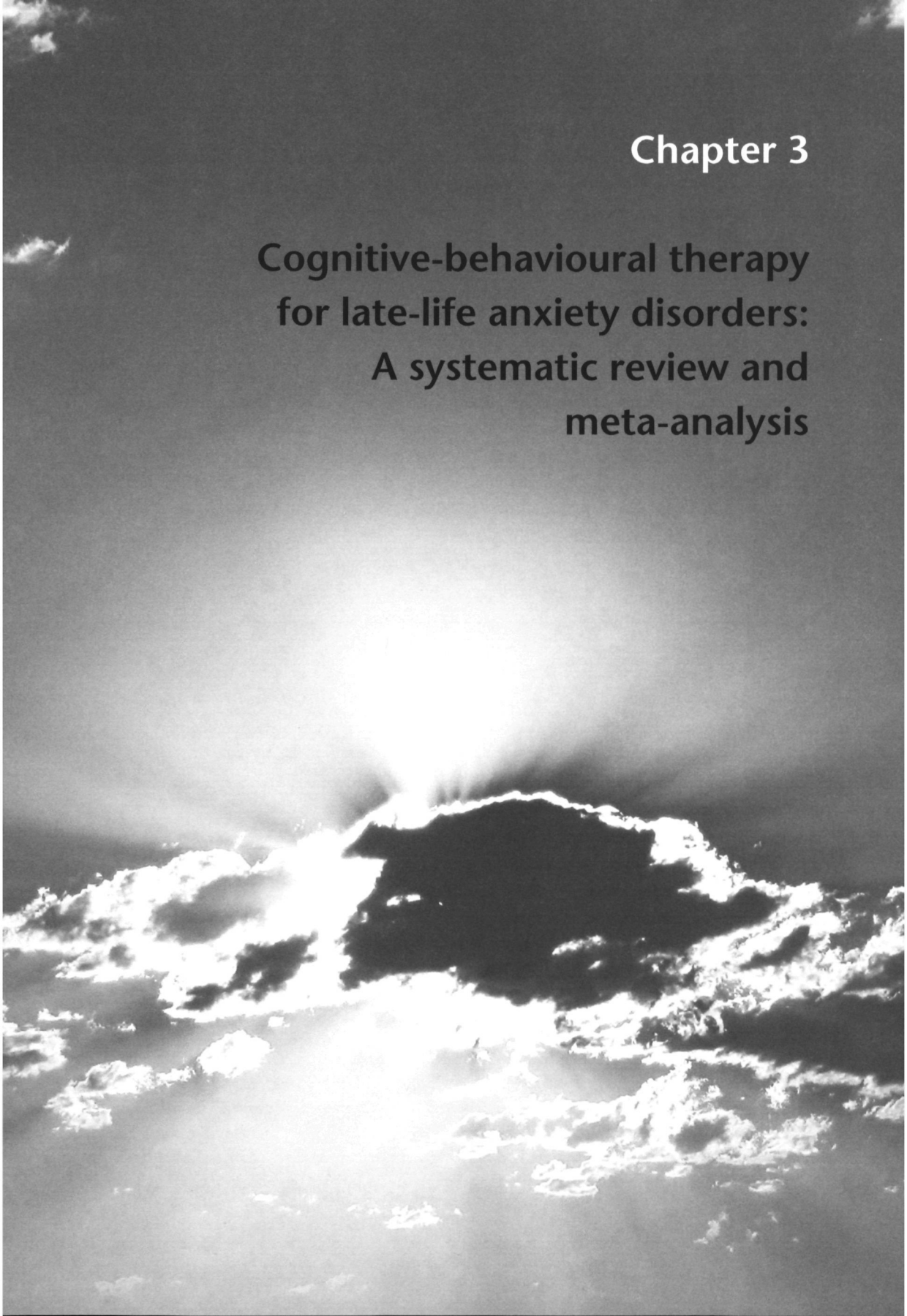
Clinical implications

Late-life anxiety disorders are common and impose a substantial burden on the patients and society at large (De Beurs et al., 1999; Van Hout et al., 2004; Wetherell et al., 2004a), which contrasts sharply with the low proportion of patients (possibly less than 10%) receiving appropriate treatment. Evidence-based guidelines for the treatment of anxiety disorders in middle-aged adults mention CBT and pharmacotherapy as the treatments of choice. On the strength of the present review we underscore the importance of adhering to these guidelines. Although these guidelines underline that CBT and pharmacotherapy with selective serotonin reuptake inhibitors (SSRIs) are preferable to benzodiazepine-based treatments since the latter may result in cognitive impairment, slip-trip-and-fall accidents, fractures and dependence or abuse (Hartikainen et al., 2007; Wang et al., 2001a; Wang et al., 2001b), one has to take into account that both the preferred SSRIs and the TCAs are associated with an increased risk of falls and hip fractures (Ensrud et al., 2002a; Ensrud et al., 2002b; French, Campbell, Spehar, Cunningham, Bulat & Luther,

2006, Hartikainen et al., 2007; Liu et al , 1998). More specifically, in view of the high prevalence of somatic symptoms like cardiovascular diseases or arthrosis in older adults and the subsequent use of other medications that could increase the risk of interaction with SSRIs (e.g. the elevated risk of gastrointestinal bleeding due to the concurrent use of aspirin or NSAIDs (Weinrieb et al., 2005; Yuan et al., 2006), we would like to advocate CBT as the optimal treatment in this population. Although proven effective in treating late-life anxiety disorders, many older patients have been found reluctant in accepting antidepressants (Givens et al., 2005). For CBT more post-treatment data are available, reflecting convincing effects, and our review revealed some promising long-term follow-up outcomes. Although the available follow-up data suggest that the effect of SSRIs is sustained when the drugs are continued (Blank, Lenze, Mulsant, Dew, Karp, Shear et al., 2006), the risk of relapse will probably be raised as a result of tapering off the drugs, which is typically not done before follow-up measurements. The follow-up data for CBT interventions, on the other hand, suggest that when CBT has been concluded, the favourable effects are sustained or may even increase, reducing the risk of relapse (Furukawa, Watanabe & Churchill, 2006; Marks, 1997; Mitte, 2006; Nadiga, Hensley & Uhlenhuth, 2003). Finally, it needs to be noted that our review uncovered high CBT dropout rates, of which therapists working in the clinical practice need to be made aware Clearly, specific attention and measures directed at preventing premature discontinuation of CBT treatment are warranted.

2.5 Final conclusion

The empirical data reported thus far show CBT and antidepressants to be most effective in the treatment of anxiety disorders in older adults. The treatments hence merit more attention and should become an integral part of the routine clinical care provided by professionals in both primary and secondary (mental) health care Based on the larger volume of data on the efficacy of CBT in late-life anxiety disorders and because of the relative risk of interaction between the dedicated drug treatment with other, concurrently used medication, the increased risks of falls and relapse risks after drug withdrawal, CBT is to be preferred over pharmacological interventions



Chapter 3

Cognitive-behavioural therapy for late-life anxiety disorders: A systematic review and meta-analysis

This chapter has been published as:

Hendriks, G J , Oude Voshaar, R C , Keijsers, G P , Hoogduin, C A L & Balkom, A J van (2008) Cognitive-behavioural therapy for late-life anxiety disorders a systematic review and meta-analysis *Acta Psychiatrica Scandinavica, 117,* 403-411

3.1 Introduction

Anxiety disorders are highly prevalent in later life affecting up to 10-15% of the independently living elderly (Beekman et al , 1998) with generalized anxiety disorder (GAD) and phobias being the most common (6-month prevalence rates 7 3% and 3 1%, respectively) However, the interpretation of these figures is hindered by the fact that pure anxiety disorders are rare as most patients have a comorbid second anxiety disorder or depressive disorder (Beekman et al , 2000, Flint, 2005a, Kessler, Chiu, Demler, Merikangas & Wolters et al , 2005b, Lenze et al , 2005a) Most older adults with anxiety disorders do not receive appropriate treatment with only 5 1% receiving psychological treatment and 3 8% being prescribed an antidepressant In contrast, the use of benzodiazepines, which are not without risk at old age, is as high as 25 8% (De Beurs et al , 1999) The negative impact of late-life anxiety on functioning, well-being and medical consumption calls for better treatment strategies (De Beurs et al , 1999, Schuurmans et al , 2005, Wetherell et al , 2005a)

Cognitive-behavioural therapy (CBT) is recommended in guidelines (APA, 2002) as an evidence-based psychological treatment for anxiety disorders in the general population (Mitte, 2005a, Mitte, 2005b, Furukawa et al , 2006, Norton & Price, 2007) Previous systematic reviews and meta-analyses of psychological treatments of anxiety in older adults, however, are methodologically flawed (Ayers et al , 2007, Nordhus & Pallesen, 2003, Pinquart & Duberstein, 2007) First, one systematic review did not include meta-analytic statistics (Ayers et al , 2007) Second, all studies also included uncontrolled trials that probably result in higher, but biased effect sizes (Nordhus & Pallesen, 2003, Pinquart & Duberstein, 2007) Third, all reviews included studies that failed to apply adequate psychiatric diagnoses by including patients with (only) subjective anxiety complaints (Ayers et al , 2007, Nordhus & Pallesen, 2003, Pinquart & Duberstein, 2007) Fourth, two meta-analytic studies did not differentiate by the content of psychological strategies by lumping all psychological treatment strategies together (Nordhus & Pallesen, 2003, Pinquart & Duberstein, 2007) Finally, none of the previous studies did differentiate studies with respect to the type of control group, while it is known that non-specific therapy factors do have significant effects and clearly differ between waiting-list control condition and any other type of control condition in which some attention is paid to patients The positive results of CBT, specifically for anxiety disorders in general, and the preferences of older adults for psychological treatment (Wetherell, Kaplan, Kallenberg, Dresselhaus, Sieber & Lang, 2004b) prompted the need for a rigorous meta-analysis of the effect of CBT for anxiety disorders in later life To overcome the limitations of previous systematic reviews and meta-analyses, we used stringent criteria for study design, patient sample and definition of CBT in this study

Aims of the study

The main objectives of this paper are 1) to provide a quantitative overview of the efficacy of cognitive-behavioural therapy (CBT) compared with a waiting-list control condition and an active control condition and 2) to provide efficacy data for the specific content of the CBT interventions

3.2 Methods

Identification of studies

To identify relevant studies we conducted a search of the Cochrane Central Register of Controlled Trials and the databases MEDLINE and PsycINFO for the period 1977 through November 2006 We used the text keywords *late-life, elderly, aged or old age* combined with the keywords *anxiety, anxiety disorder, panic disorder, generaliz(s)ed anxiety disorder, social anxiety disorder, and social phobia,* and the keywords *therapy, psychotherapy, treatment, psychological treatment, cognitive treatment, or behavio(u)r(al) treatment* This search strategy was repeated using the MESH-terms *aged, aged, 80 and over, anxiety disorder (exploded) and psychotherapy (exploded)* and subsequently extended by a manual search of the reference lists of all resultant randomized controlled trials evaluating psychological treatment(s) for late-life anxiety disorders

Inclusion criteria

Reports meeting the following criteria were included in the meta-analysis

a Use of a randomized controlled research design,

b Inclusion of patients with a mean or median age of at least 60 years,

c Patients diagnosed with generalized anxiety disorder, panic disorder, social phobia, or agoraphobia according to the ICD-9, ICD-10, DSM-III, DSM-IIIR or DSM-IV and verified by a (semi-)structured clinical interview as these are the most prevalent anxiety disorders in later life, with high mutual comorbidity rates (Kessler et al , 2005a, Kessler et al , 2005b),

d Inclusion of a treatment arm with cognitive-behavioural therapy, defined as a protocol-based psychological treatment including at least psycho-education, relaxation training, cognitive restructuring of irrational and maladaptive anxiety beliefs and exposure to anxiety provoking situations,

e Results for anxiety, worry and/or depression presented separately for each treatment arm, and

f Use of valid outcome measures (self-report questionnaire or clinical interview)

The first two authors (G J H and R C O V) independently checked the inclusion and exclusion criteria of the identified studies Excluded were outcome studies without a

randomized controlled design (e.g. open trials, case-series and case reports), review papers, and studies including mixed adult and elderly people. Publication in languages other than English was no exclusion criterion.

Selection procedure, data extraction and quality assessment

The first two authors subsequently coded the selected studies separately. Discrepancies in the two coding forms were resolved by consensus after discussion or by referring to the data in the original article, yielding one coding form per article consisting of the following items: year of publication, total number of patients included, number of completers and dropouts, diagnosis, diagnostic criteria, duration of the disorder, age, sex, type of treatment, duration of the treatment, presence and duration of follow-up, outcome measures and the results on post-treatment outcome measures of interest (see analyses) and finally type of control condition. Control conditions were classified as either a waiting-list or an active control condition during which patients received (specific) attention. The active control condition was defined as comprising either treatment as usual or any other strategies that provided a contact frequency comparable to the CBT condition.

The methodological quality of the included studies was also independently assessed using the Amsterdam-Maastricht consensus list ranging from 0 [poor quality] to 19 [excellent quality] and covers the Chalmers criteria usually applied in the assessment of study quality (Chalmers et al., 1981, Van Tulder et al., 1997). The Amsterdam-Maastricht consensus list is accepted by the Cochrane Review Group (Van Tulder et al., 1997) and has been used previously in systematic reviews of randomized controlled trials in psychiatric disorders (Oude Voshaar et al., 2006; Van Boeijen et al., 2005).

Statistical analysis

The primary outcome measure was the severity of anxiety. Secondary outcome measures were the severity of worrying, which is a common feature of anxiety disorders not specific for generalized anxiety disorder, and depressive symptoms, which often occur in patients with anxiety disorders (Starcevic, Berle, Milicevic, Hannan, Lamplugh & Eslick, 2007). To control for non-specific effects of attention paid to the patients and their symptoms, analyses were conducted separately for studies with a waiting-list control condition and those with an active control condition. We a priori decided to use the Beck Anxiety Inventory (Beck et al., 1988a) and, if not available, the Hamilton Anxiety Rating Scale (Hamilton, 1959) for anxiety; the Penn State Worrying Questionnaire (PSWQ) (Meyer et al., 1990) and, if unavailable, the Worry Domain Questionnaire (WDQ) (Van Rijsoort, 1999) for worrying; and finally, the Beck Depression Inventory (Beck, 1988b) and, if unavailable, the Center for Epidemiological Studies rating scale for Depression (CES-D) (Radloff, 1977) for depressive symptoms.

In contrast to the previous systematic reviews and meta-analyses (Ayers et al., 2007; Nordhus & Pallesen, 2003; Pinquart & Duberstein, 2007) data were analyzed with RevMan 4.2 (Cochrane statistical software). At the moment Cochrane methodology is widely advised and accepted as the preferred method in meta-analytic studies. We used the standardized mean difference (SMD) as the summary statistic in our meta-analysis, which expresses the size of the treatment effect in each trial relative to the variability observed in that trial, enabling us to pool different scales assessing one outcome measure. The SMD thus reflects the difference in the mean outcome between groups divided by the standard deviation of outcomes among participants. We applied the chi-square test for heterogeneity, and because the number of included studies was small a p-value < 0.10 was considered significant (Cochrane handbook for systematic reviews of interventions 4.2.5. The Cochrane Collaboration, 2005, pp. 135). We used a fixed effect model if homogeneity was found and a random effect model if not (although the latter model slightly compromised the statistical power of our analysis). As most studies only presented data of those participants who had completed the trial (Figs 3-1 and 3-2), summary statistics are based on available case analyses. For an adequate interpretation, dropout numbers per study and treatment condition are reported separately Publication bias was explored by preparing funnel plots for all outcome measures.

3.3 Results

Search strategy

The initial search yielded 959 reference titles in a combined search in MEDLINE and PsycINFO and 111 in the Cochrane Library of which 56 titles were identified as having possible relevance to the treatment of late-life anxiety disorders by G.J.H or R.C.O.V. After screening of the abstracts and the full text, we excluded 49 papers. The reasons for exclusion were No RCT (n = 38); no proper diagnostic procedures (n = 7); evaluation of pharmacotherapy only (n = 3); inadequate study design (n = 1). The following seven papers met the inclusion criteria: Barrowclough et al. (2001), Mohlman et al. (2003), Schuurmans et al. (2006), Stanley et al. (1996), Stanley et al. (2003a), Stanley et al. (2003b), Wetherell et al. (2003) As Mohlman et al. (2003) described two different pilot trials, we considered these as two separate studies designated as a and b. Furthermore, as Wetherell et al. (2003) randomized patients over three conditions, viz. CBT, a discussion group and a waiting list, we used their CBT outcomes both vis-à-vis the results of the waiting-list and the active control condition. The study by Schuurmans et al. (2006) did only report change-scores, but this study could be included as the authors kindly provided their end-of-treatment scores on request of the researchers.

Study quality

Appendix 3-A lists the scores for methodological quality of the studies as assessed with the Amsterdam-Maastricht consensus list. The sum score (range 0-19) is taken to reflect study quality but since neither patients nor therapists can be blinded to a psychological treatment condition, the maximum score in psychotherapy studies is 17. The narrow range from 12 to 15 indicates a moderate to good study quality without major differences between studies. Inter-rater discrepancies were limited to a one point difference in three of seven studies.

Study characteristics

The study characteristics are summarized in Table 3-1 by type of control condition. The four trials that compared CBT with a waiting-list condition comprised a total of 146 patients with a mean age of 68 years of whom 73% were women. Thirty-two patients (22%) dropped out prematurely; 23 (26%) patients in the CBT condition and 9 (16%) in the waiting-list condition ($\chi^2 = 1.81$; df = 1, $p = 0.18$). The five trials comparing CBT and an active control condition included 243 patients with a mean age of 69 years of whom 77% were women. Sixty patients (25%) dropped out before the outcome assessment; 35 (28%) patients in the CBT condition and 25 (21%) in the active control condition ($\chi^2 = 1.70$; df = 1, $p = 0.19$).

Table 3-1. Study characteristics of all studies reviewed

Study	Number of patients			Sex	Mean	Primary	No. of	Group
	Included	Dropouts	Completers	female	age	diagnosis	sessions	therapy
	n	*n*	*n*	%	(years)			
Mohlman et al (2003)	27	6	21	70%	66	GAD	13	No
Mohlman et al. (2003)	15	-	15	60%	68	GAD	13	No
Wetherell et al. (2003) *	49	10	39	80%	67	GAD	12	Yes
Schuurmans et al. (2006)	55	16	39	73%	70	GAD, PD, AG, SP**	15	No
Total CBT vs. waiting list	146	32	114	73%	68			
Stanley et al. (1996)	48	17	31	71%	68	GAD	14	Yes
Barrowclough et al (2001)	55	12	43	77%	72	GAD, PD, SP, AD-NOS***	8 - 12	No
Stanley et al. (2003b)	12	3	9	83%	71	GAD	8	No
Stanley et al. (2003a)	85	21	64	75%	66	GAD	15	Yes
Wetherell et al. (2003) *	52	16	36	80%	67	GAD	12	Yes
Total CBT vs. active control	250	67	183	77%	69			

* This study had a three-condition design evaluating CBT with active control and waiting list and was therefore included in both meta-analyses.

** GAD: 35%; PD: 40%; AG without history of PD: 13%; SP: 13%.

***GAD: 19%; PD: 51%; SP: 2%; AD-NOS: 28%.

Abbreviations: GAD = generalized anxiety disorder; PD = panic disorder with and without agoraphobia; SP = social phobia; AD-NOS = anxiety disorder not otherwise specified; AG = agoraphobia

Most studies included patients with a primary diagnosis of GAD only. However, two studies also included patients suffering from panic disorder, social phobia or anxiety disorder not otherwise specified (Barrowclough et al. 2001; Schuurmans et al., 2006). All studies allowed a comorbid diagnosis of anxiety and affective disorder (limited to major depression and dysthymia) provided that the anxiety disorder was the primary diagnosis. The active treatment phase ranged from 8 to 15 weekly sessions, delivered either in a group format (4 comparisons) or individually (5 comparisons). The active control condition involved minimal contact including weekly telephone calls and consultation on demand (Stanley et al., 2003a), usual care (Stanley et al., 2003b), supportive psychotherapy (Barrowclough et al., 2001; Stanley et al., 1996), and a discussion group (Wetherell et al., 2003).

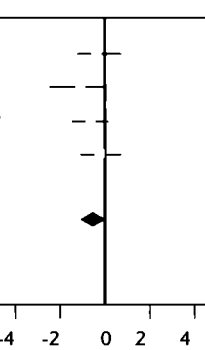
Meta-analyses

The results for the primary outcome variable, level of anxiety, of the two analyses are presented in Figures 3-1 and 3-2.

Figure 3-1. The effects of cbt versus waiting-list control conditions on the level of anxiety in patients over 60 years

Review: Cognitive-behavioural therapy for anxiety disorders in later life
Comparison: 01 CBT versus waiting list
Outcome 01 Effect on anxiety level

Study or sub-category	N	Treatment Mean (*SD*)	N	Control Mean (*SD*)	SMD (fixed) 95% CI	Weight %	SMD (fixed) 95% CI
Mohlman et al. (2003a)	11	10.25(7 03)	10	11 45(4.87)		21 34	-0 19 [-1 05, 0 67]
Mohlman et al (2003b)	8	-1 35(1 00)	7	1 65(3 41)		12 45	-1.16 [-2 29, -0 04]
Wetherell et al (2003a)	18	12 90(9.60)	21	19 10(10 90)		37 89	-0.59 [-1.23, 0.06]
Schuurmans et al (2006)	30	14 34(12 85)	9	15 67(8 72)		28 32	-0.11 [-0 85, 0.64]
Total (95% CI)	67		47			100 00	-0 44 [-0 84, -0 04]
Test for heterogeneity χ^2 = 2 88, df = 3 (p = 0.41), I^2 = 0%							
Test for overall effect Z = 2 17 (p = 0 03)							



The four studies comparing CBT with a waiting-list condition and the five comparing CBT with an active control condition were all homogeneous with respect to the primary outcome parameter (p = .41 and p = 0.12, respectively) and yielded a pooled standardized mean difference of -0.44 [95% CI: -0.84, -0.04] and -0.51 [95% CI: -0.81, -0.21] in favour of the CBT condition (Z = 2.17; p < .05 and Z = 3.32; p <.001, respectively).

Figure 3-2 The effects of CBT versus active control conditions on the level of anxiety in patients over 60 years

Review: Cognitive-behavourial therapy for anxiety disorders in later life
Comparison: 02 CBT versus waiting list
Outcome 01 Effect on anxiety level

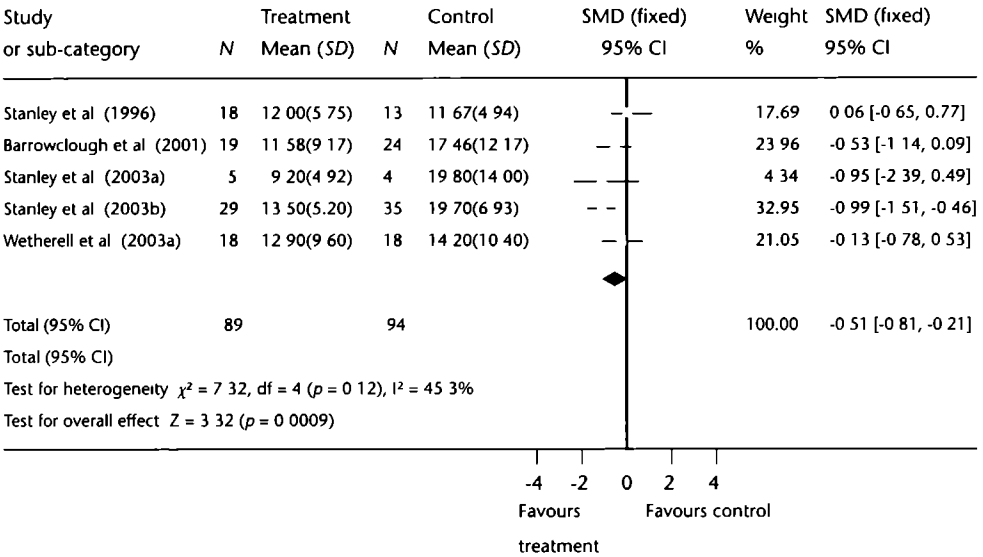


Table 3-2 presents the summary statistics of the meta-analyses for the two secondary outcome measures. The CBT versus waiting-list comparisons were also homogeneous both with respect to their effect on worrying (p = 0.58) and on depression (p = 0.35). For both outcome measures, the pooled effect of CBT was superior to that of the waiting-list condition (see Table 3-2). The analyses of the CBT versus active control studies generated homogeneous results for depression, again demonstrating a significant superior effect for CBT after pooling. The results relating to worrying were, however, heterogeneous (p

Table 3-2. The effect of CBT on worrying and depressive symptoms associated with late-life anxiety disorders

	No. of patients		Test for	Pooled standardized	p-
	CBT	Control	heterogeneity	mean difference [95% CI]	value
CBT versus waiting-list control condition					
Worrying	54	47	χ^2 = 1.97; df = 3; p = 0.58	-0.57 [-0.97, -0.17]	.005
Depression	54	47	χi^2 = 3.32; df = 3; p = 0.35	-0.54 [-0 94, -0.14]	.008
CBT versus active control condition					
Worrying	70	70	χi^2 = 7.34; df = 3; p = 0.06	-0.54 [-1.13, 0.04] *	.07
Depression	89	94	χ^2 = 7.62; df = 4; p = 0.11	-0.35 [-0.64, -0.05]	.02

* A random effect model was applied to correct for the heterogeneity as indicated by a significant (p < .10) test for heterogeneity

= 0.06). Subsequent application of a random effect model did not yield any significant effects, although it did reveal a trend in favour of CBT (p = 0 07).

Due to the limited number of studies included and comparable effect sizes in both comparison groups (i.e. comparison with a waiting-list control condition or an active control condition), we prepared funnel plots for all studies together. The funnel plots were asymmetrical for all outcome measures (anxiety, worrying and depression) due to one small study by Stanley et al. (2003b). Excluding this study did not affect the outcome.

3.4 Discussion

Main findings

The present meta-analysis shows the efficacy of CBT in the treatment of anxiety disorders (as based on DSM-IV criteria) occurring later in life. Not only was its efficacy demonstrated in various samples of over-60s when compared to a waiting-list condition, it was also shown relative to an active control condition. The same magnitude of the effect size in both comparisons contrasts with our expectation that the effect of CBT would be greatest with respect to the waiting-list control condition. These differences are caused by the high effect sizes of both studies by Stanley et al. (2003a, 2003b), which might be explained by a lower impact of non-specific therapy factors due to the relative short duration of therapist-patient contact in both control conditions of these studies This explanation, however, is not consistent with the fact that the effect sizes of these studies are also much higher compared to three of the four trials that included a waiting-list control condition. Therefore, in our opinion the same magnitude of the effect size in both comparisons is most likely explained by the low number of studies in both analyses, which may lead to a high impact of individual studies.

Interestingly, CBT also proved significantly superior in its effect on the concurrent symptoms of worrying and depression, although, relative to the active control conditions its outcome on worrying did not reach significance (p = .07). This latter lack of effect may be attributable to the fact that power was reduced due to exclusion of the study by Barrowclough et al. (2001), which did not provide outcome data for worrying. This explanation seems plausible, because the effect size they report for anxiety was similar to the size we generally found for worrying.

Methodological considerations

The main limitation of the current meta-analysis is the limited number of eligible studies and the relatively small sample sizes that were used, which makes the results prone to publication bias. Although the funnel plot is not conclusive, it is also not suggestive for

publication bias. Interestingly, all individual authors of the included studies argued in favour of the efficacy of CBT, while our analyses yielded only significant results in 2 out of 9 trials by analysing them on outcome measures only (as proposed by the Cochrane Collaboration, see Figs 3-1 and 3-2). This can be explained by baseline differences between the CBT and control groups with more severely affected patients in the CBT conditions. As the analyses were completer-based, this might suggest both, biased randomization procedures or selective dropout (although the actual number of dropouts did not differ significantly between the CBT and control conditions). Nevertheless, their assertions are corroborated by significant results obtained by pooling the individual trial outcomes, which indicates the importance of meta-analysis in this field of research. However, the small number of studies, the lack of data for different diagnostic groups, and most importantly, high comorbidity rates precluded subgroup analyses for the separate anxiety disorders Two studies included a population suffering from mixed anxiety disorders, while the other studies included patients with GAD. Because all studies had high comorbidity rates with other anxiety disorders and depression and outcome measures were not specific for diagnostic categories, as presented in Table 3-1, we considered these differences as minimal. However, since the majority of the studies were limited to older patients suffering from at least GAD, the present findings may be most generalizable to older GAD patients. Considering that GAD is the most prevalent anxiety disorder in later life, our meta-analysis nevertheless underscores the importance of CBT in this growing part of the general population.

Finally, with our a priori exclusion criteria we eliminated reports that had not adhered to valid diagnostic procedures at baseline, thus having ensured that the patients assessed were in actual fact suffering from a psychiatric disorder and not from non-specific anxiety complaints due to a variety of temporary stressors and that the anxiety disorder indeed was the primary diagnosis.

Clinical implications

Since late-life anxiety disorders are common and significantly reduce quality of life, adequate treatment strategies are urgently needed. Yet, the prevalence rates of adequate treatment contrast sharply with the estimates of less than 10% of the over 60s receiving appropriate treatment for their complaints. Our results confirm that CBT may be an adequate treatment strategy for this elderly patient group. Many elderly people resist the use of antidepressants based on fear of dependence, prior negative experiences, resistance to viewing their symptoms as a medical illness, and concern that antidepressants will prevent natural feelings (Givens et al., 2006). From a clinical point of view, the high prevalence of somatic syndromes such as cardiovascular diseases and arthrosis in the elderly and the subsequent use of medications increase the risk of interaction with selective serotonin reuptake inhibitors (SSRIs) The concurrent use of SSRIs and

aspirin or NSAIDs (Weinrieb et al., 2005; Yuan et al., 2006), for example, raises the risk of gastrointestinal bleeding. Finally, the evidence for the efficacy of antidepressants for late-life anxiety disorders is limited with only three valid randomized controlled trials published thus far (Katz et al., 2002; Lenze et al., 2005; Schuurmans et al., 2006). CBT may also be a viable, more constructive alternative for those elderly patients that are currently being prescribed benzodiazepines or antidepressants for their anxiety, as longer-term use of benzodiazepines and antidepressants can result in a 1.4 to 2.4 fold increased risk for cognitive impairment, slip-and-fall accidents, fractures and dependence or abuse (Ensrud et al., 2003; French et al , 2006, Kurzthaler, Warnbacher, Golser, Sperner, Sperner-Unterweger & Haidekker et al., 2005; Liu et al., 1998; Paterniti et al., 2002; Wang et al., 2001a). However, some difficulties can occur in conducting CBT to older people. The elderly tend to discuss their problems more in terms of physical symptoms, seem to have difficulties in applying cognitive techniques and in adhering strictly to the CBT protocol (Hyer, Kramer & Sohnle, 2004; Rainsford, 2002; Schuurmans et al., 2006). To enhance outcome it is advised to give special attention in establishing a strong therapeutic alliance, pay particular attention to motivating strategies to empower patients to overcome their, most often, longstanding complaints, include extra sessions for psycho-education, give special attention to doing homework, contacting family, and visiting patients at home (Barrowclough et al., 2001; Mohlman et al., 2003, Stanley et al., 2003a; Wetherell et al., 2003; Hyer et al., 2004)

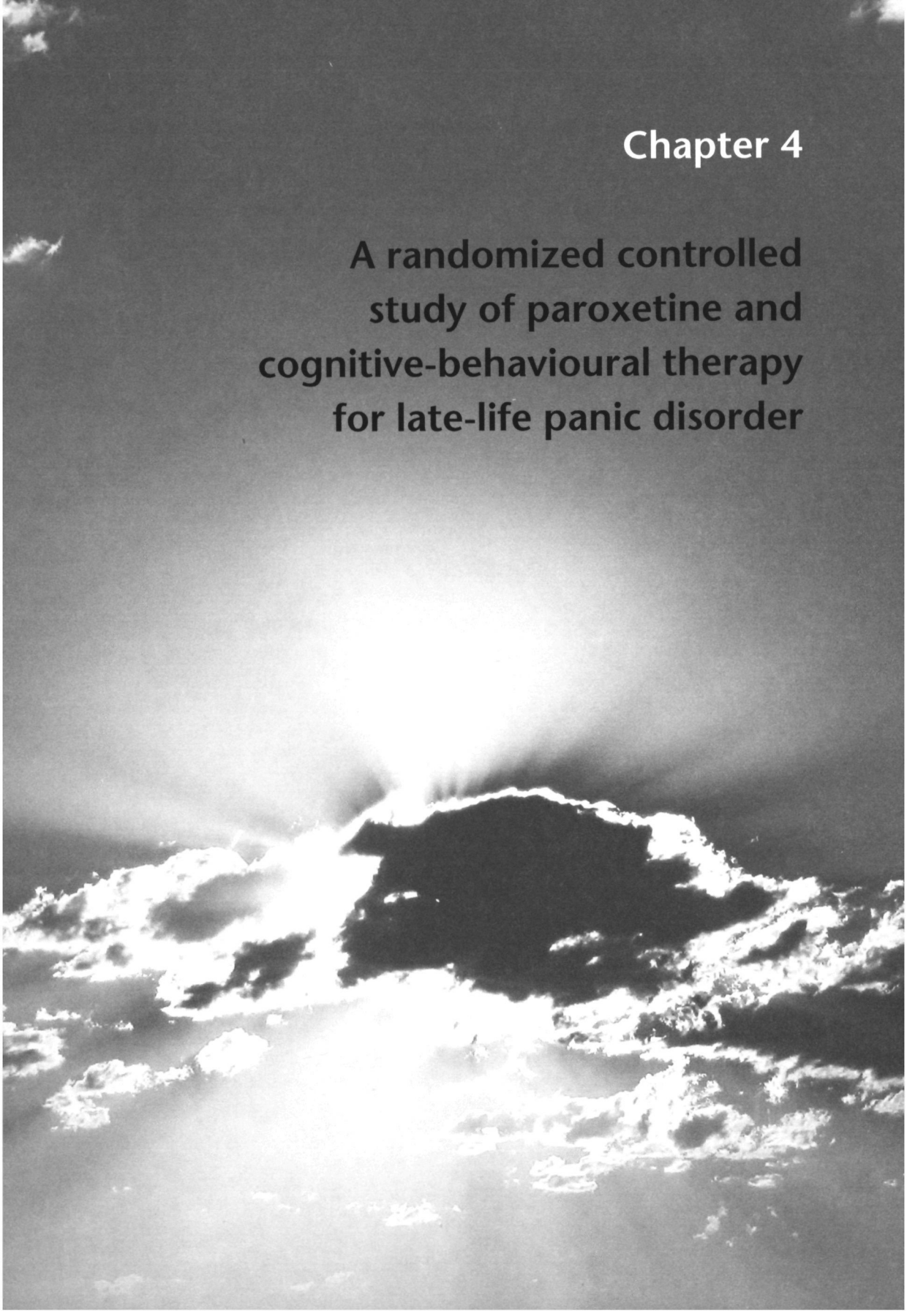
Because of the lack of follow-up data for the control conditions, we could not include CBT follow-up data in our formal meta-analysis. Nonetheless, 5 of the 7 studies reporting follow-up data showed a further decline of anxiety levels (Barrowclough et al., 2001; Mohlman et al., 2003; Stanley et al., 1996; Stanley et al., 2003a; Wetherell et al., 2003), whereas 2 trials reported a minimal increase (Barrowclough et al., 2001; Mohlman et al., 2003), which is similar to longer-term CBT-efficacy studies in adult patients (Barlow, Gorman, Shear & Woods, 2000; Bockting, Spinhoven, Koeter, Wouters, Visser & Schene, 2006; Furukawa et al., 2006; Marks, 1997; Mitte, 2005b; Mitte, 2006; Nadiga et al., 2003; Norton & Price, 2007).

Final conclusion

Cognitive-behavioural therapy is an effective, evidence-based therapy for adults over 60 suffering from anxiety disorders, which therefore deserves more research and more attention in the routine clinical care of both primary health-care workers (general practitioners, social workers) and secondary mental health-care professionals.

Appendix 3-A. Validity scores of the studies evaluated according to the Amsterdam-Maastricht consensus list

Study	Stanley et al. (1996)	Barrowclough et al. (2001)	Mohlman et al. (2003)	Stanley et al. (2003b)	Stanley et al. (2003a)	Wetherell et al. (2003)	Schuurmans et al. (2006)
Validity criteria							
Adequate randomization procedure	+	+	+	+	+	+	-
Concealed random allocation of treatments	-	+	-	-	-	-	+
Baseline similarity tested	+	+	+	+	+	+	+
Control for co-interventions in design	-	-	+	+	+	+	+
Check for adherence to interventions	+	+	+	-	+	+	-
Valid outcome measures	+	+	+	+	+	+	+
Relevant outcome measures	+	+	+	+	+	+	+
Outcome assessor blinded	0	+	+	-	+	+	-
Therapist blinded	0	-	0	-	0	0	0
Patient blinded	0	-	0	-	0	0	0
Withdrawals and dropouts (proportion; inequality between groups; reasons for withdrawal/dropout reported)	+	+	+	+	+	+	+
Identical timing of outcome assessment for all intervention groups	+	+	+	+	+	+	+
Intent-to-treat analyses	-	-	-	-	+	+	+
Descriptive criteria							
Specification of eligibility criteria	+	+	+	+	+	+	+
Description of interventions	+	+	+	+	+	+	+
Follow-up	+	+	+	-	+	+	+
Adverse events	0	0	0	+	0	0	+
Statistical criteria							
Sample size: to be presented at randomization and outcome	+	+	+	+	+	+	+
Presentations of point estimates and distribution measures	+	+	+	+	+	+	+
Total score (range 0-19)	12	14	14	12	15	15	14



Chapter 4

A randomized controlled study of paroxetine and cognitive-behavioural therapy for late-life panic disorder

A revision of this chapter has been resubmitted for publication to *Acta Psychiatrica Scandinavica:*

Hendriks, G.J., Keijsers, G.P.J., Kampman, M., Oude Voshaar, R.C., Verbraak, M J.P M , Broekman, T.G. & Hoogduin, C.A.L. A randomized controlled study of paroxetine and cognitive-behavioural therapy for late-life panic disorder.

4.1 Introduction

Even though the estimated life-time prevalence of panic disorder with or without agoraphobia (PD(A)) seems lower in elderly people compared to younger and middle-aged adults, it is still as high as 2% (Kessler et al., 2005a). In later life the effects of ageing become increasingly more pronounced and heterogeneous, not only deepening the differences between younger and older adults, but also those between the elderly themselves. Yet, possibly due to ageism, relatives often interpret anxiety symptoms and avoidance behaviour in an elderly person as normal and more or less acceptable while he or she may be suffering from a phobic disorder (Lindesay, 1991). As a result of the ageing process itself somatic morbidity increases and may partially overlap certain panic and anxiety symptoms (Hocking & Koenig, 1995). In addition, panic physiology and anxiety cognitions tend to decline with increasing age and in the elderly in whom the onset of PD(A) occurs beyond the age of 60 years specific symptoms usually are less severe than they are in younger patients (Flint, Koszycki, Vaccarino, Cadieux, Boulenger & Bradwejn, 1998, Segui et al., 2000; Sheikh et al., 2004a). Based on these findings, some authors characterized PD(A) in later life as a less severe disorder (Segui et al., 2000; Sheikh et al , 2004a).

By contrast, agoraphobic symptoms do not seem to decline with age (Segui et al., 2000). Compared to panic attacks and anxiety cognitions, agoraphobia, moreover, is more susceptible to improvement following treatment in younger PDA adults and may be more reliable and valid in reflecting symptom severity (Basoglu, Marks, Kilic, Swinson, Noshirvani, Kuch et al., 1994; De Beurs, Lange, Van Dyck & Koele, 1995). For a subgroup of elderly patients with an onset at an older age, the agoraphobic symptoms may, however, be less severe than in younger adults suffering from the disorder, while in elderly patients with disease onset at a younger age the phenomenology may initially have been more disguised due to overlapping, comorbid somatic disorders dampening panic physiology and an environment that is more tolerant towards agoraphobic behaviour. These changes may hinder appropriate diagnosing of PD(A), leaving older patients undiagnosed and untreated. In fact, in clinical practice less than 10% of the elderly suffering from anxiety disorders is offered psychological treatment or antidepressant therapy while more than 25% is prescribed benzodiazepines, which is clearly not the treatment of choice (De Beurs et al., 1999) The consequences of late-life anxiety disorders going undiagnosed and untreated are large. Recent findings showed that late-life anxiety has a tendency to become chronic and is associated with a substantial risk of major depression, increases in health-care consumption, reduced quality of life and more disability (Beekman et al., 2000; Brenes et al., 2007; De Beurs et al., 1999; Schuurmans et al., 2005; Wetherell et al., 2004a; Wetherell et al., 2005).

Well-developed and evidence-based treatment algorithms for PD(A) are available

in guidelines (e g NICE[1]) but research findings are limited to adult populations aged between 18 and 65 years and the number of randomized controlled trials (RCTs) investigating late-life anxiety disorders is modest Although restricted to studies on generalized or mixed anxiety disorders, recently published meta-analytic reviews of the use of cognitive-behavioural therapy (CBT) and antidepressants in the treatment of elderly patients showed both approaches to be effective, with a suggested advantage of antidepressants over CBT (Hendriks et al , 2008a, Pinquart & Duberstein, 2007) However, with 9-18% in the younger aged patients and 27% in the older patients dropout rates were relatively higher for CBT in the elderly patients, which suggests a relative and age-related intolerance of CBT in elderly patients suffering from anxiety disorders (Hendriks et al , 2008a, Pinquart & Duberstein, 2007, Mitte, 2005a, Mitte 2005b) In contrast, with 23-25% in the younger aged patients and 22% in the elderly patients, the overall dropout rates for pharmacotherapy were comparable in both age groups (Hendriks et al , 2008a, Pinquart & Duberstein, 2007, Mitte, 2005a, Mitte 2005b) In short, it remains unclear from mentioned reviews whether the recommendations in the guidelines for the treatment of PD(A) can be extrapolated to older PD(A) patients

To date, only three studies, viz a randomized, placebo-controlled pilot study of imipramine and alprazolam (Sheikh & Swales, 1999), an open CBT study (Swales et al , 1996), and one open study of sertraline (Sheikh, Lauderdale & Cassidy, 2004b), have specifically tested treatment outcomes for late-life PD(A) Two trials reported dropout rates, 28% (n = 7) prematurely left the study in the pharmacotherapy trial (Sheikh & Swales, 1999) and in the CBT study 25% (n = 5) dropped out (Swales et al , 1996) The third study with 10 participants (Sheikh et al , 2004b) reported no dropout rates None of the studies mentioned specific age-related factors to explain dropout In the completers both pharmacotherapy and CBT were well tolerated and effective Investigating mixed anxiety-disorder populations (Barrowclough et al , 2001, Schuurmans et al , 2006), two studies also reported on substantial proportions of patients with late-life PD (51% and 45%, respectively) Although again CBT and pharmacotherapy were both found to be effective, these studies were also hampered by dropout rates (22% (n = 12) and 32% (n = 27), respectively) as well as a lack of specified outcome measures for PD Thus, because of the relatively large dropout rates, the limited sample sizes, and the absence of well-delineated PD outcome measures the conclusions of these studies also failed to provide definitive answers

To help resolve these inconclusive findings, we conducted an RCT in patients aged over 60 years that were all diagnosed with PD(A) in accordance with the well-established guidelines for younger adults More specifically, we examined the effects of individual CBT and an SSRI (paroxetine) relative to a waiting-list control group To our knowledge, ours is the first trial to do so exclusively in this age group

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Aims of the study

The main objectives of our RCT were: i) to examine the effectiveness of paroxetine and a protocolized, individual CBT originally developed for younger adults in elderly patients suffering from panic disorder and to compare the outcomes to those obtained in patients on a waiting list, ii) to compare the effectiveness of paroxetine with protocolized, individual CBT, and iii) to examine the feasibility of both treatment arms

4.2 Material and methods

Patient selection

Eligible were all adults aged over 60 years with a principal diagnosis of panic disorder (PD) or PD with agoraphobia (PDA) (APA, 1994) undergoing treatment in our outpatient clinic specialized in the treatment of anxiety disorders. All patients were referred by their primary care physician. Exclusion criteria were the presence of severe psychiatric disorders (e.g. psychotic disorder, bipolar disorder), a severe somatic condition that would hinder appropriate application of CBT (e.g. severe cardiovascular disease), a contraindication for paroxetine, current use of an antidepressant in an adequate dose, current and adequate psychological treatment, failure of paroxetine or CBT in the past, abuse of or dependency on alcohol or psychoactive substances, dementia, and a score of 23 or less on the Mini-Mental State Examination (Folstein, Folstein & McHugh, 1975). Comorbidity with other anxiety disorders, depression or dysthymia was allowed as long as PD(A) was the principal diagnosis. Participants using benzodiazepines were asked to adhere to a fixed daily dose for the duration of the study (also see the Procedure and Treatment sections).

Procedure

After referral to our outpatient clinic all patients took part in two intake sessions at week -2 and week 0 during which the PD(A) diagnoses were verified using the Dutch version of the Anxiety Disorders Interview Schedule-Revised (ADIS-IV), which was administered by independent and trained assessors (DiNardo et al., 1994; Bouman et al., 1997). Following confirmation of the diagnoses and an oral description of the study, written informed consent of the patients was obtained after which they were randomly assigned to one of the three study conditions according to a 2:2:1 schedule To this end, a sealed envelop was selected from an initial total of 75 envelopes containing the treatment assignments, with 30 being labelled as 'CBT', 30 as 'paroxetine' and 15 as 'waiting list'. The randomization schedule was based on the assumption that the waiting-list condition would show no effects (Wetherell et al., 2003). The patients allocated for treatment subsequently took the first baseline assessment by completing several self-

report questionnaires (see below). They completed the same instruments again at week 8, week 14 (coinciding with CBT completion), and week 26 (the 3-month post-treatment follow-up). Patients assigned to the waiting-list condition were also first assessed immediately following randomization, and subsequently at weeks 8 and 14, after which they were offered their preferred treatment (CBT or antidepressant). They were not further tested for the present study. As these patients were in need for treatment a waiting-list condition up to week 26 was not allowed by the Medical Ethical Review Board of the University Medical Centre of Nijmegen.

Instruments

Anxiety cognitions and phobic avoidance were the primary outcome measures and were evaluated using the Dutch adaptations (De Beurs, 1993) of the Agoraphobic Cognitions Questionnaire (ACQ) (Chambless, Caputo, Bright, & Gallagher, 1984) and the Mobility Inventory Avoidance scale (MI-A) (Chambless, Caputo, Jasin, Gracely & Williams, 1985). The original instruments have frequently been used in PD treatment outcome studies.

The ACQ consists of 14 items that have to be rated on a 5-point rating scale and aims to assess the severity of catastrophic agoraphobic cognitions. Good reliability estimates have been reported, with test-retest correlations varying between 0.71-0.86 and a Cronbach's alpha varying between 0.72-0.84 (29, 30). In our sample with elderly people, the Cronbach's alpha was 0.63, which is lower than reported for younger age samples.

The MI gauges the severity of phobic avoidance of 27 situations using two subscales: avoidance when alone (MI-AAL) and avoidance when accompanied (MI-AAC), and one subscale consisting of 1 item to assess the frequency of panic attacks (MI-PF). Good test-retest reliability (r varies between 0.76-0.90) and Cronbach's alpha (range 0.91-0.97) have been reported (29, 31). In our population, the Cronbach's alpha was 0.93 for the MI-AAL and 0.94 for the MI-AAC, similar to those reported in younger age samples. The MI-PF gives a definition of panic attacks according to the DSM-IV followed by a question inquiring about the number of panic attacks that occurred during the past seven days. As the frequency of panic attacks is largely dependent on the level of avoidance behaviour and given that avoidance behaviour is associated with the severity of PDA (Basoglu et al., 1994a; De Beurs et al., 1993), we opted to use the total MI-A mean scores for our analyses (Kampman, Keijsers, Hoogduin & Hendriks, 2002). A patient was classified as being panic-free when he/she reported zero panic attacks during the preceding week. As a panic-free status does not correspond with improvement on the ACQ or the MI-A, we used this dimension as a secondary outcome measure (Van Balkom, Spinhoven, Bakker, Rammeloo, Graatsma, Adriaanse et al., 2000).

General psychopathology was assessed as the additional secondary outcome measures using the Dutch version of the Symptom Checklist (SCL-90) (Arrindell & Ettema, 1986; Derogatis, Rickels & Rock, 1976). The SCL-90 is a frequently used outcome measure

with good psychometric properties (Arrindell & Ettema, 1986; Derogatis et al., 1976).

Treatment feasibility was determined using a proxy variable, i.e., the proportion of patients that withdrew prematurely from either CBT or paroxetine treatment. All assessments were administered by trained, independent psychologists who were blind to the study and treatments delivered.

Treatment

During the 26-week study period concomitant treatment was not allowed, while patients taking benzodiazepines (oxazepam or equivalent agents) were kept at a fixed dose of 10 mg/d.

Individual CBT consisted of 14 weekly sessions of fifty minutes each consistent with Craske and Barlow (Craske, Meadows & Barlow, 1994). The standardized programme comprised the following five components: (1) education about panic and anxiety, (2) relaxation techniques, (3) interoceptive exposure, (4) cognitive therapy, and (5) exposure in vivo. After the 14th session CBT was tapered off within a maximum of 6 sessions during the 12-week follow-up period.

Patients in the paroxetine condition were treated according to a fixed-dose schedule. The daily 10 mg starting dose in week 1 was increased with 10 mg a week to 40 mg/d in week 4, during which period patients were seen during 30-minute weekly consultations. To control for any adverse events and to encourage patients to adhere to the treatment protocol, from week 5 to week 14 all patients attended five 30-minute medical consultations once every two weeks during which their queries were addressed and information about the expected (side) effects of the treatment was provided. Paroxetine was maintained in a 40 mg/d dosage during weeks 14 to 26.

Therapists

The therapists were all psychologists trained at the master of science level with extensive experience in cognitive-behavioural techniques for adults with PD(A) Throughout the study they were weekly supervised by a registered supervisor (a member of the Dutch Association of Behavioural and Cognitive Therapy). Per session the therapists recorded which specific CBT component they had applied and any deviations from the treatment manual were discussed. Adaptations to the specific circumstances of the patients were allowed (e.g. adapting interoceptive exposure exercises to the physical condition of the patient in case of COPD), provided they did not conflict with the manual. In the paroxetine condition patients were seen by a (resident) psychiatrist.

Statistical analysis

Outcome scores were analyzed using a mixed-model procedure, which allows all available data for all subjects to be entered into the analyses, preventing the loss of subjects for whom

data were incomplete and thus precluding ad-hoc (e.g. 'last observation carried forward') solutions. We analyzed our outcome variables using the MIXED procedure in SPSS with the Conditions (paroxetine, CBT, and WL) and Time (week 0, week 8, week 14, week 26) as the main fixed effects, Condition by Time as the interaction factor, and the Patients as the random effects within Time. The random effect covariance matrix was specified as unstructured, implying it had no restrictions imposed on it. The SPSS mixed-model procedure provides Estimated Marginal Means (EMM), which are model-predicted means that allow easy testing of custom hypotheses contrasts. Instead of testing the main effect of the Condition factor, we were a priori interested in two custom contrasts: the Paroxetine-WL and the CBT-WL contrasts both at week 14. Further, and by post hoc analyses, we investigated Paroxetine-CBT contrasts at weeks 8, 14, and 26. Paroxetine-WL and CBT-WL contrasts were investigated by computing *t*-values for the differences in the EMMs. For the post-hoc Paroxetine-CBT contrasts Sidak's adjustment for multiple comparisons was used. For clinical interpretation we calculated the pre-post Cohen's *d* effect size per treatment condition, as well as the baseline corrected between-group Cohen's *d*. Furthermore, we analyzed the proportion of patients that improved more than 30% on one of the primary outcome scales, as an improvement of 30% on disorder specific anxiety scales indicates a clinically relevant improvement (Bandelow, 2004; Bandelow et al., 2006).

Changes in panic-free ratios were analyzed using the Wilcoxon Signed Rank Test for Paired Comparisons. Effects were considered statistically significant at $p < .05$. The Statistical Package for the Social Sciences (SPSS) 15.0 was used for all analyses (SPSS inc., 2006).

4.3 Results

A total of 153 older adults reporting anxiety symptoms that had been referred to our outpatient clinic were screened. Ninety-four patients were excluded as they did not meet the inclusion criteria (no principal diagnosis of panic disorder according to DSM-IV criteria, $n = 85$; interfering medications, $n = 9$; history of treatment with CBT, $n = 0$, previous treatment with paroxetine, $n = 0$) and another 10 patients refused randomization. The remaining 49 patients fulfilled all criteria and were randomly assigned to one of the three study conditions (see Table 4-1). Comorbidity was common: 33 (67.3%) patients suffered from a chronic somatic disorder, with 23 (46.9%) patients having a cardiovascular disease and 5 (10.2%) a chronic obstructive pulmonary disease, while 14 (28.6%) patients had a comorbid psychiatric diagnosis: 7 (14.3%) patients were diagnosed with another anxiety disorder, 6 (12.2%) with a mood disorder, and 3 (6.1%) with a somatoform disorder. Although there was a significant group difference for psychiatric

Table 4-1. Baseline patient characteristics for the three conditions (individual CBT, 40 mg/d paroxetine, and 14-week waiting list)

Variable	CBT (n = 20)	Paroxetine (n = 17)	Waiting list (n = 12)	Total (n = 49)	Test statistic	p
Age M (*SD*)	69.6 (5.0)	68.8 (4.3)	66.8 (4 2)	68.6 (4.6)	$F(2,46) = 1.38$	26
Duration of anxiety (yrs) M (*SD*)	12.3 (14.2)	12.3 (17.5)	18.4 (16 5)	13.8 (15.8)	$F(2,46) = .662$	.52
Female *n* (%)	11 (55.0)	10 (58.8)	9 (75.0)	30 (61.2)	$\chi^2(2) = 1.33$	.515
Living alone* *n* (%)	10 (50 0)	6 (35.3)	3 (25.0)	19 (38.8)	$\chi^2(2) = 2.11$	.349
Education *n* (%)					$\chi^2(8) = 4.54$	.81
Low *n* (%)	6 (30.0)	6 (35.3)	5 (41.7)	17 (34.7)		
Medium *n* (%)	9 (45 0)	6 (35.3)	4 (33.3)	19 (38.8)		
High *n* (%)	5 (25 0)	5 (29.4)	3 (25.0)	13 (26.5)		
PD with agoraphobia *n* (%)	20 (100)	16 (94.1)	12 (100)	48 (97.9)	$\chi^2(2) = 1.92$	.38
Comorbid psychiatric diagnosis** *n* (%)	2 (10.0)	8 (47.1)	4 (33.3)	14 (28.6)	$\chi^2(2) = 6.36$	.04
Comorbid somatic disorder*** *n* (%)	12 (60.0)	13 (76.5)	8 (66.7)	33 (67.3)	$\chi^2(2) = 1.14$	.57
Oxazepam 10 mg (or equivalent) *n* (%)	6 (30.0)	7 (41 2)	9 (75.0)	22 (44.9)	$\chi^2(2) = 6.28$	.04
ACQ (*SD*)	1.6 (0.5)	1.8 (0.4)	1.7 (0.4)	1.7 (0.5)	$F(2,46) = .34$	.68
MI-A (*SD*)	2.4 (1.0)	2.3 (0.8)	2.72 (1.2)	2.4 (1.0.	$F(2,44) = .71$	.50
SCL-90 (*SD*)	168.4 (48.6)	166.8 (27.4)	171.10 (43 2)	168.4 (39 8)	$F(2,43) = .04$	.97

* widow/widower, divorced, never married

** anxiety disorder, depression and/or somatoform disorder

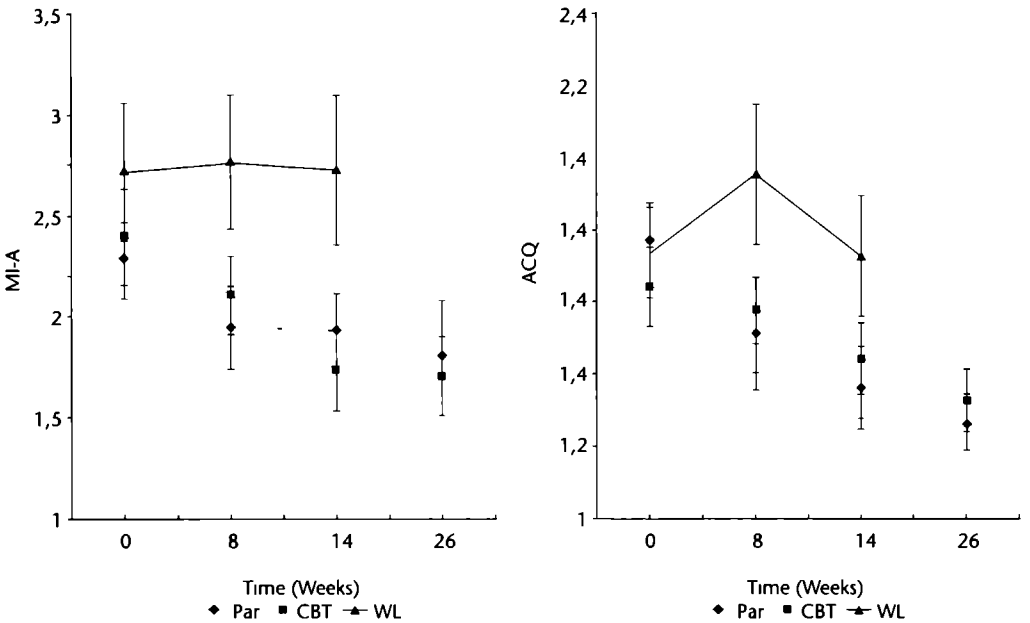
*** mostly cardiovascular diseases (n = 23) or chronic obstructive pulmonary diseases (n = 5)

PD = Panic Disorder; ACQ = Agoraphobic Cognitions Questionnaire; BDI = Beck Depression Inventory; MI-A = Mobility Inventory Avoidance scale; SCL-90 = Symptom Checklist

comorbidity (in favour of the paroxetine condition), there were no significant between-group differences on the SCL-90 sum scores or any of the outcome measures reflecting the severity of the underlying psychiatric diagnoses. No between-group differences were found for patient demographics.

Five patients (10.2%) failed to complete the 14-week treatment protocol: three dropped out in the paroxetine condition (side effects, n = 1; protocol violation, n = 1; broken hip, n = 1), one in the CBT condition (protocol violation), and one in the WL condition (severe somatic illness). Another three patients (6.1%), two treated with paroxetine and one with CBT, refused further participation in the follow-up assessment at week 26 (see Figure 4-1). In the CBT condition eight patients terminated treatment immediately after succesfully completing the protocolized 14 weekly sessions and consulting their therapist. In 12 patients CBT was tapered off in 4.2 (*SD* = 1.8) sessions on average. All 11 patients assigned to the waiting-list control condition chose CBT as their treatment of choice after their waiting-list period was concluded.

Figure 4-1. Changes in the Mobility Inventory (MI-A) total score & Agoraphobic Cognitions Questionnaire (ACQ) total score



Abbreviations PAR = paroxetine, CBT = cognitive-behavioural therapy, WL = waiting list

Compared to the ACQ scores obtained in the WL condition, the 8- and 14-week scores were significantly improved both for the paroxetine (t (44) = -2 32, p < 05 and t (44) = -2 43, p < 05, respectively) and the CBT condition (t (42) = -2 14, p < 05 and t (43) = -2 02, p = 05 respectively), which also held for the MI-A scores with t (48) = -2 50, p < 05 and t (46) = -2 56, p < 05 for the paroxetine and t (47) = -2 23, p < 05 and t (45) = -3 36, p < 01 for the CBT group Furthermore, Table 4-2 and Figure 4-1 show that the improvements achieved with CBT and paroxetine were sustained (and actually further slightly improved) at the 26-week follow-up Both the baseline corrected Cohen's ds for between-group effects (compared to the WL condition) as the Cohen's ds for within-group effects for the primary outcomes (ACQ, MI-A) were moderate-to-large for both treatment arms compared to the WL condition Furthermore, a clinically relevant improvement was found for 7/14 (50%) paroxetine treated patients, for 9/18 (50%) CBT treated patients and for 1/10 (9%) patients assigned to the waiting-list control condition (χ^2 (2) = 5 7, p = 057) (Table 4-2)

Table 4-2. Mean scores and standard deviations for all outcome measures at weeks 0 to 26 and treatment versus waiting-list effect sizes at week 14 per condition

	Baseline		End of treatment	Follow-up	Within-group Cohen's *d*		Between-group Cohen's *d*
Condition	Week 0	Week 8	Week 14	Week 26	Week 14	Week 26	Week 14
Paroxetine							
ACQ, mean (*sd*)	1.8 (0 4)	1.5 (0.4)	1.4 (0.4)	1.3 (0.3)	1.0	1.4	0.9
MI-A, mean (*sd*)	2.3 (0.8)	1.9 (0.8)	1.9 (0.7)	1.8 (1.0)	0.5	0.6	0.4
SCL-90, mean (*sd*)	166.8 (27.4)	145.7 (28.6)	135.9 (24.8)	133.1 (29.0)	1.2	1.2	0.8
CBT							
ACQ, mean (*sd*)	1.6 (0.5)	1.6 (0.4)	1.4 (0.4)	1.3 (0.4)	0.4	0.7	0.4
MI-A, mean (*sd*)	2.4 (1.0)	2.0 (0.9)	1.7 (0.9)	1.7 (0.8)	0.7	0.8	0.7
SCL-90, mean (*sd*)	168.4 (48.6)	159.6 (42.6)	145.4 (32.8)	143.4 (32.7)	0.6	0.6	0 5
Waiting list							
ACQ, mean (*sd*)	1.7 (0 4)	1.9 (0.6)	1.7 (0.6)		0		
MI, mean (*sd*)	2.7 (1.2)	2.8 (1.1)	2 7 (1.2)		0		
SCL-90, mean (*sd*)	171.1 (43.2)	176.6 (49.3)	169.7 (52.0)		0		

Abbreviations: ACQ = Agoraphobic Cognitions Questionnaire, MI-A = Mobility Inventory Avoidance scale, SCL-90 = Symptom Checklist.

The two treatments also showed better results on the secondary outcome measures relative to the WL scores: a significant change was found for the SCL-90 in the paroxetine condition at week 14 (t (45) = -2.18, $p < .05$) but the change in the CBT condition did not reach significance (t (44) = -2.00, $p = .052$)

With the mixed-model procedure yielding p-values ranging between .54 and .97, the post-hoc comparisons of the 14- and 26-week outcome effects of both active treatments did not reveal any statistically significant differences for any of the measures

Because fluctuations in the frequency of the self-reported panic attacks were large across all measurements – probably due to variations in avoidance behaviour or recall bias – we used, in line with previous research (Kampman, Keijsers, Hoogduin & Hendriks, 2002) the proportion of patients that had not experienced any panic attacks the week prior to the relevant assessment as a qualitative measure to evaluate treatment efficacy and defined it as the panic-free ratio (Figure 4-1). At week 14 the panic-free ratio in the paroxetine condition had increased significantly from 23.5% (n = 4) to 86% (n = 12; t = -2.83, $p < .05$), which improvement was sustained at week 26 (83%, n = 10 (t = -2 45, $p < .05$). Although not significantly, in the CBT condition the baseline-to-14-week ratio had risen from 55% (n = 11) to 72% (n = 13; T = -1.41, $p = .16$) and had improved further at follow-up (78%, n = 14; t = -1.89, $p = .06$). The panic-free ratio for the WL showed no change (baseline 42% (n = 5); 14 weeks: 46% (n = 5); t = 0, p = 1.0). Both paroxetine and CBT were well tolerated as only four patients withdrew from treatment due to intolerance.

Entering oxazepam or equivalent agent as a fixed factor in the mixed-model analyses did not show any significant effect of benzodiazepine use. Nor did the results change when correcting for the number of psychiatric comorbid conditions at baseline.

4.4 Discussion

Main findings

The results of our study, the first RCT to test two treatment approaches for late-life panic disorders with or without agoraphobia, supported our hypotheses that both protocolized CBT and paroxetine are effective and well-tolerated treatments for elderly patients. Previous RCTs that primarily studied patients with generalized late-life anxiety disorders reported attrition rates between 20% and 30% (Hendriks et al., 2008a; Pinquart & Duberstein, 2007). With only three patients (17.6%) prematurely ending pharmacotherapy because of intolerance and one (5%) abandoning CBT because of significant stress caused by daily home work and exposure exercises within the first 14 weeks of the trial, our study showed both treatments to be well tolerated. Scores for phobic avoidance (MI) and catastrophic agoraphobic cognitions (ACQ), indicative of PD severity, showed statistically significant reductions in both treatment conditions. As benzodiazepines were only allowed in one prescribed low fixed dose throughout the study, the observed reductions in symptoms cannot be attributed to these agents. Further, with respect to the WL condition, the between-group effect sizes were satisfactory for both paroxetine and CBT, ranging from 0.6 to 0.9. These results are consistent with those of previous studies examining the efficacy of SSRIs or CBT for late-life anxiety disorders (Hendriks et al., 2008a; Pinquart & Duberstein, 2007) and are comparable to those found (i.e. 0.7) in a recent meta-analysis in younger PD(A) populations (Haby, Donnelly, Corry & Vos, 2006)

The panic-free ratio improved significantly in the patients receiving paroxetine but not in the patients receiving CBT It is important, however, to emphasize that in both treatment conditions almost 80% of the patients were panic-free at the 26-week follow-up. Both treatments also revealed reduced general psychopathological symptoms (SCL), with paroxetine showing a significant effect and CBT a trend (p = .052) towards significance.

Strengths and limitations

We used a protocol-based and guideline-recommended CBT in an individual format that was specifically targeted at PD(A) although not expressly adapted to elderly patients. There is abundant empirical evidence supporting PDA-specific, individual CBT (Mitte, 2005a).

Although it is assumed that age-specific adaptations may help increase the efficacy of CBT for late-life anxiety (Stanley et al., 2003a) here, also, empirical evidence is scarce. Two, albeit small-scale trials testing dedicated CBTs for generalized anxiety disorders indeed showed superior outcomes. A pilot study found primary-care CBT that was specifically adapted to older patients to be more effective in improving worry and depression than treatment as usual (Stanley et al., 2003b) and another trial that directly compared a standard and an enhanced, age-adapted CBT also concluded that the latter approach seemed to increase treatment efficacy (Mohlman et al., 2003).

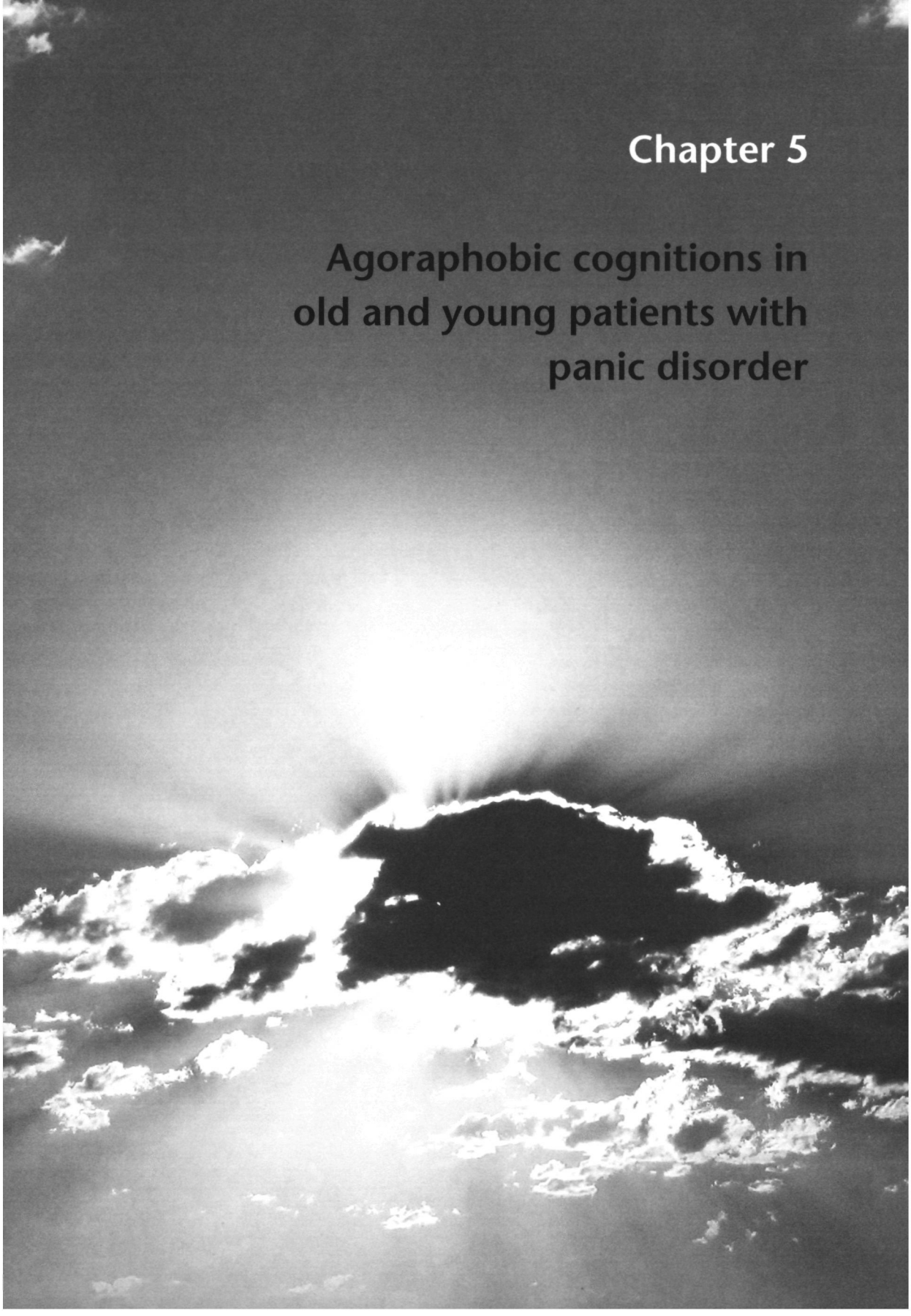
Several critical remarks about our study are warranted. Firstly, small group sizes cannot prevent between-patient differences from being equally divided across the various groups. However, correcting for these differences did not change our results.

Secondly, the self-report instruments we used to evaluate treatment effects in our PD(A) patients have been validated in younger populations (18-65 yrs) only, which may imply that the scales are less valid for older patients, such as our 60-plus cohort. Validation studies in 60-plus samples are scarce, but the available results showed few objections for their use in this age range (Fuentes & Cox, 2000; Crittendon & Hopko, 2006) Nevertheless, the findings for anxiety cognitions in our elderly PD(A) patients are modest. The only study comparing the ACQ in older and younger patients found lower baseline scores for the older patients (Sheikh et al., 2004a). In fact, the scale may be less suitable for assessing anxiety cognitions in elderly PD(A) patients. However, validated instruments for assessing agoraphobic cognitions in elderly PD(A) patients are not available yet. Observer-rated instruments like the Panic Disorder Severity Scale (PDSS; Shear, Rucci, Williams, Frank, Grochocinski, Vander et al., 2001) or the Panic Agoraphobia Scale (PAS; Bandelow, Broocks, Pekrun, George, Meyer, Pralle et al., 2000) may be more appropriate but, until now, neither were examined in elderly PD(A) patients. Thirdly, we did not repeat formal diagnostic procedures post-treatment. Therefore, we are not able to report how many patients still met DSM-IV criteria of panic disorder post-treatment. However, in both treatment conditions half of the patients achieved a clinically relevant improvement, against only 9% in the control condition.

Based on our and earlier findings and connotations and given the need for additional research into late-life PD in larger cohorts, we wish to offer several recommendations for future research As observational instruments such as the Panic Disorder Severity Scale (Shear et al., 2001) and the Panic Agoraphobia Scale (Bandelow et al., 2000) are now available in various languages, we recommend them as the preferred tools or advise their use to complement other (self-report) scales to establish treatment efficacy in this population. Secondly, as elderly patients tend to be averse to the use of antidepressants (Givens et al., 2006) and prefer behavioural and cognitive therapies (Wetherell et al., 2004b), research into how treatments can best be tailored to their needs and preferences

is indispensable. Finally, because we found no relevant differences in the effects of antidepressant treatment and CBT, further efficacy studies are required to establish which of the two treatment arms is most effective, especially when CBT is tailored to 60-plus patients.

In conclusion, despite its drawbacks and pending corroboration, but comparable to earlier reports on younger adults, the present study suggests that both the SSRI paroxetine and CBT are effective in the treatment of PD in elderly patients.



Chapter 5

Agoraphobic cognitions in old and young patients with panic disorder

A revision of this chapter has been resubmitted for publication to the *American Journal of Geriatric Psychiatry:*

Hendriks, G.J., Keijsers, G.P.J., Kampman , M., Oude Voshaar, R.C. & Hoogduin, C.A.L Agoraphobic cognitions in old and young patients with panic disorder.

5.1 Introduction

It has been suggested that elderly people tend to report less severe cognitive anxiety than younger individuals (Brenes, 2006; Crittendon & Hopko, 2006; Goldberg et al., 2003), which may be attributable to a natural, age-related decrease in emotional responsiveness, i.e., a dampening of affective reactivity (Gross et al., 1997; Lau et al., 2001). If true, one would expect elderly respondents to have lower scores on self-report instruments measuring the severity of cognitions related to the disorder under study. To date, only one study directly compared the frequency or severity of agoraphobic cognitions of younger and older adults diagnosed with panic disorder (PD) and it indeed showed the older patients to have significantly fewer agoraphobic cognitions (Sheikh et al., 2004a). These findings have to be interpreted with caution, however, as most self-report instruments were developed for younger patients and might thus be less applicable in later life as the content of agoraphobic cognitions may change with age (Griez et al., 2007). To substantiate this assumption, in this study we analyse age-related effects at the item level using the scores of PD patients on the Agoraphobic Cognitions Questionnaire (ACQ).

5.2 Method

We ran a cross-sectional analysis of the data we obtained from patients suspected of panic disorder with agoraphobia (PDA) that were referred to our specialized outpatient anxiety clinic. Exclusion criteria were the current use of an antidepressant or a primary psychiatric diagnosis of a psychotic, bipolar or substance use disorder, or dementia. A comorbid diagnosis of another anxiety disorder, depression or dysthymia was allowed as long as PDA was the primary diagnosis. All patients who consented to the present study received a baseline assessment in which a primary diagnosis of PDA was confirmed using the Anxiety Disorders Interview Schedule-Revised (ADIS-IV; Bouman, et al , 1997; DiNardo et al., 1994). The ADIS-IV was administered by independent and trained assessors. Subsequently, the confirmed patients completed several self-report instruments among which the two we analyzed for this study.

The severity of catastrophic cognitions was assessed using the 14-item Agoraphobic Cognitions Questionnaire (ACQ; Chambless et al , 1984; De Beurs, 1993), with each item to be rated on a 5-point scale. The inventory may be scored as a total scale, or according to its two subscales Loss of Control and Physical Concerns, each comprising 7 items. The subscale scores or total score are calculated by averaging the responses on the individual items composing that score. The ACQ is well validated in both the English and the Dutch version, yielding good test-retest reliability, high internal consistencies,

and reasonable concurrent validity (De Beurs, 1993; Chambless et al., 1984).

The Mobility Inventory Avoidance scale (MI-A; Chambless et al., 1985) was used to assess agoraphobic avoidance as a proxy of PDA severity (Basoglu et al., 1994a; De Beurs et al., 1993).

Statistical differences between the two age groups (see below) were analyzed using student *t*-tests (ACQ total and subscale scores) and the item comparisons were performed using a Mann-Whitney U-test. Effects were tested two-sided. In order to correct for multiple testing, a Bonferroni correction was applied. Results were considered significant at $p < .004$ (05 / 14 items). *p*-values between .05 and .004 are considered to reflect a potentially interesting trend. The SPSS 16.0 statistical analysis package was used (SPSS inc, 2008).

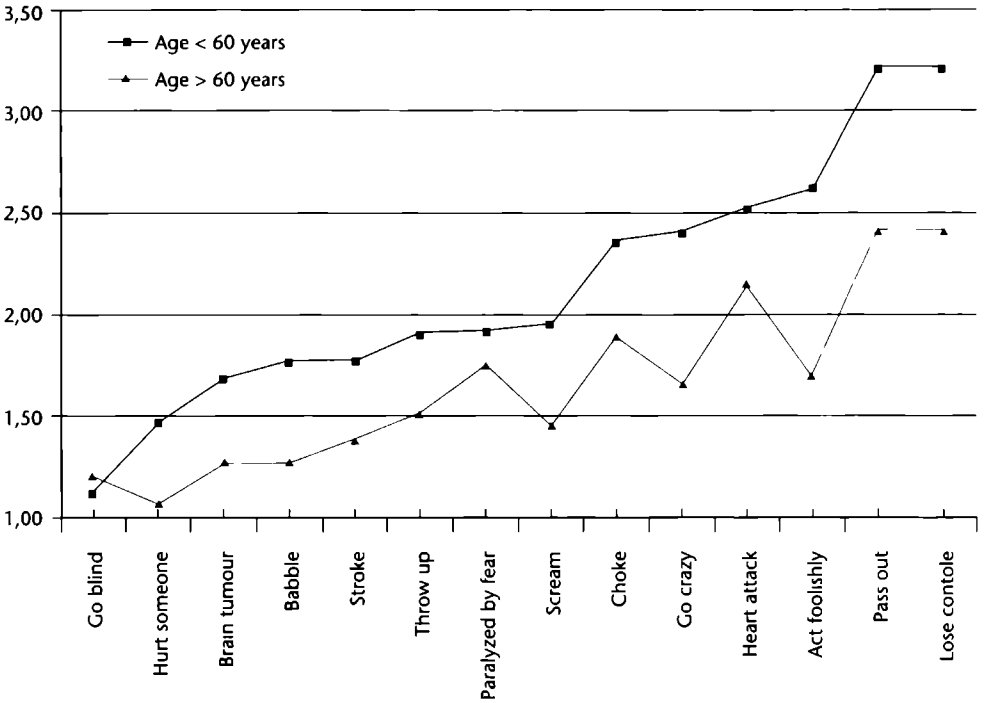
5.3 Results

A total of 205 confirmed PDA patients were included and evaluated in two age groups 157 patients in the 18-to-60-year group (mean age: 35 years, *SD*:10) and 48 patients in the 60-plus group (mean age: 68 years; *SD*: 5). The groups did not differ with respect to sex (male: 36% vs. 35%; $\chi^2 <$. 01, df = 1, $p = .98$) or duration of illness (DOI: 12.1 (15.6) vs. 7.7 (9.3) years; $t = -.73$, df = 202, $p = .47$). Please note that the *t*-test was performed after log transformation of the DOI in order to normalize the skewed distribution of this variable. PDA severity also did not differ between the age groups given that their levels of MI agoraphobic avoidance were similar (mean MI score 2.4; *SD* 0.9) vs. 2.4 (0.8); $t = -.028$, df = 202, $p = .78$).

The mean (*SD*) ACQ total score was significantly lower in the older patients (1.6 (0.5) vs. 2.1 (0.6); $t = 5$ 7, df = 203, $p < .001$). Similar results were found for the Loss of Control subscale (1.6 (0.6) vs. 2.2 (0.9); $t = 4.3$, df = 203, $p < .001$) and Physical Concerns subscale (1.6 (0.5) vs. 2.1 (0.6); $t = 4.5$, df = 203, $p < .001$).

Figure 5-1 presents the mean scores for the 14 ACQ items in order of increasing severity as observed in the younger age group. Apart from scoring numerically lower on the total scores, the item order for the 60-plus patients also differed from the order we found for the younger respondents, with the items fear of screaming, going crazy, and acting foolishly being less prevalent in the late-life PDA group. Five items (fear of going crazy, acting foolishly, passing out, losing control, and brain tumours) showed a clear, statistically significant age-related difference ($p < .004$), six items (fear of throwing up, choking, hurting someone, getting a stroke, screaming, babbling) a trend towards significance ($.004 < p < .05$), while three items (fear of a heart attack, going blind, and being paralyzed by fear) showed no statistical difference ($p > .05$).

Figure 5-1. ACQ-item scores in order of increasing severity in elderly and younger patients



5.4 Discussion

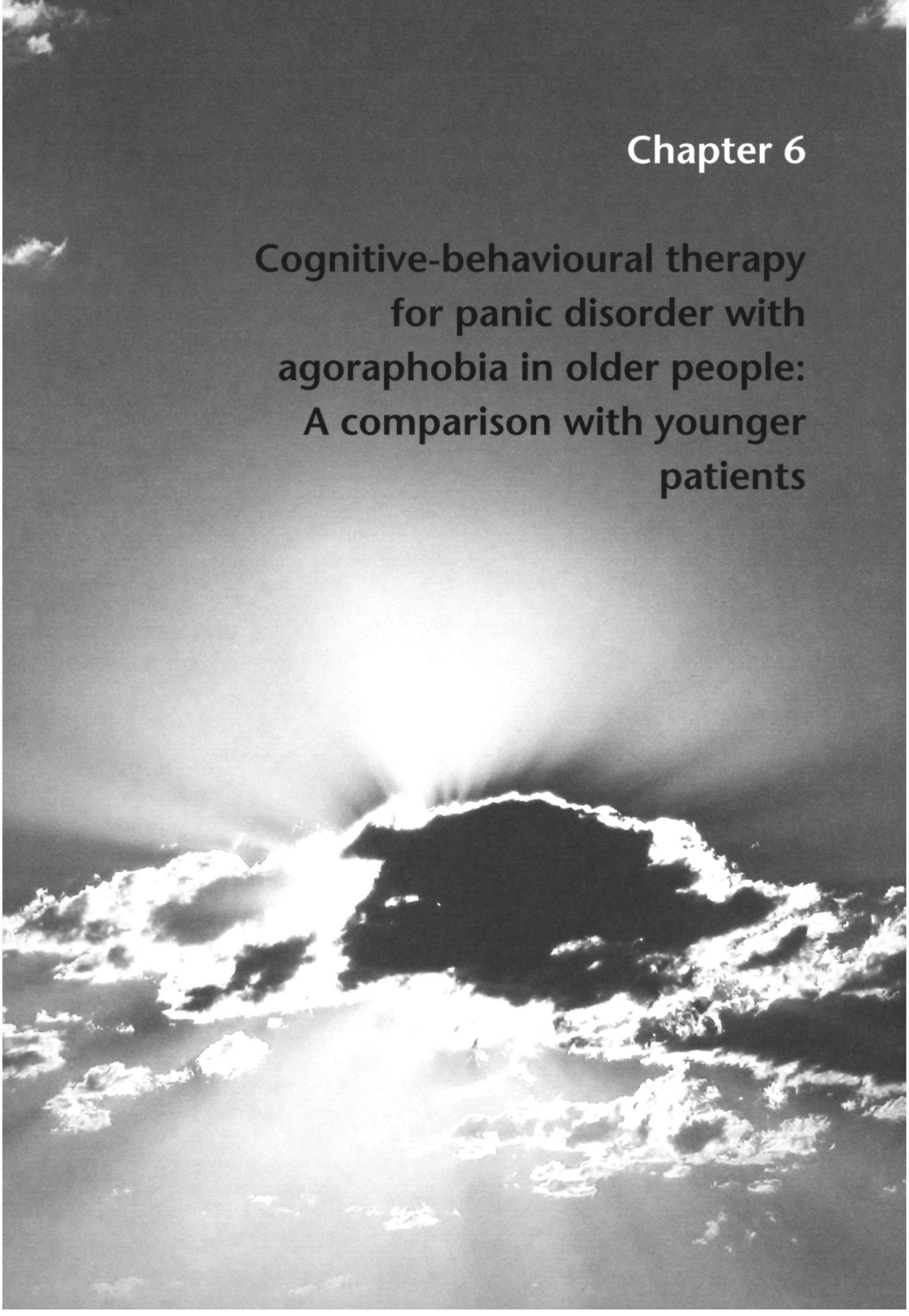
Comparing younger and older patients with agoraphobic panic disorder, we found that the severity of agoraphobic cognitions in the 60-plus patients was significantly lower than the levels obtained in their younger counterparts, whereas MI agoraphobic avoidance, the major measure of PDA severity, did not differ between the two age groups. The only study to also directly compare the ACQ in older and younger PDA patients had found similar, lower scores in the older patients (Sheikh et al., 2004a).

Comparing the age groups at the ACQ item level, we found only three items that were scored comparably by the younger and older respondents, i.e., the classic anxiogenic cognition of getting a heart attack and the cognitions of fear of becoming blind (with low prevalence rates in both age groups, probably reflecting a floor effect) and becoming paralyzed.

But what are the underlying mechanisms explaining these age-related differences? Firstly, the largest differences occurred in the fear of losing control, going crazy, and acting foolishly items, which may indicate an age-related decrease of the lesser 'loss of control' cognitions. In view of the outcomes of a carbon dioxide challenge test in healthy

controls, Griez et al. (2007) found it plausible that thoughts of losing control during panic attacks decline with age. Secondly, the fact that the catastrophic cognitions relating to physical concerns (which may become much more realistic in later life) were also less severe in the 60-plus group suggests that elderly patients are indeed less inclined to interpret physical symptoms as catastrophic. Both explanations hence seem to suggest that PDA in later life is less severe in its manifestations than it is in younger adults.

Yet, agoraphobic avoidance, the most important indicator of PDA severity, did not differ between our two age groups, which would point to a third mechanism: as the agoraphobic avoidance had run a longer, chronic course in the 60-plus patients, an age-related change in other agoraphobic cognitions seems more likely. However, we cannot substantiate this postulation as we did not perform a qualitative analysis of cognitions that are not incorporated in the ACQ and that might have been more prevalent in the older patients and thus significantly more related to their agoraphobic avoidance patterns Such an analysis would be especially relevant for the development of an age-sensitive instrument gauging agoraphobic cognitions. Based on our current and earlier findings, and until new, age-sensitive tools are devised, we would recommend health professionals to rely on the severity of agoraphobic avoidance when assessing the extent of agoraphobic panic disorder in older adults.



Chapter 6

Cognitive-behavioural therapy for panic disorder with agoraphobia in older people: A comparison with younger patients

This chapter has been submitted for publication:

Hendriks, G J , Kampman, M , Keijsers, G P J , Verbraak, M J P M , Oude Voshaar, R C & Hoogduin, C A L Cognitive-behavioural therapy for panic disorder with agoraphobia in older people A comparison with younger patients

6.1 Introduction

Even though 2.8% of the elderly population suffer from panic disorder with or without agoraphobia (PD(A); Grant, Hasin, Stinson, Dwason, Goldstein, Smith et al., 2006), few treatment studies of PD(A) in later life are available. This is especially worrying as late-life anxiety disorders are associated with elevated health-care consumption, lowered quality of life and more (severe) disability (Beekman et al., 2000; De Beurs et al., 1999; Schuurmans et al., 2005; Wetherell et al., 2004b). Cognitive-behavioural therapy (CBT) and antidepressants have empirically been well established and are commonly effective treatments for PD(A) (Furukawa et al., 2006; Mitte, 2005a), but belonging to an older age group seriously decreases the likelihood of actually receiving these recommended treatments (Wang et al., 2005a) In fact, less than 10% of the elderly suffering from an anxiety disorder is offered psychological treatment or is prescribed an antidepressant (De Beurs et al., 1999)

The undertreatment of late-life anxiety disorders may be explained by the low referral rate for targeted treatment, which is three times lower than the rate for late-life major depression (17% versus 55%; Ettner & Hermann, 1997). Also the assumption that in the elderly anxiety disorders constitute only a minor health problem that does not require (explicit) treatment may hinder appropriate referral and treatment (Wetherell et al., 2005a). More specifically, in clinical practice many therapists consider manualized CBT inappropriate, being convinced that patients need personalized treatment plans adapted to their individual needs, with which stance they undermine CBT in specific target groups like elderly PD patients. Empirical evidence for these assumptions, however, is hardly available (Wilson, 1996). As older patients generally prefer psychological treatment over drug therapy (Givens et al., 2006) and physicians generally fear adverse drug events in elderly people, further research into the effects of CBT in late-life anxiety disorders is needed.

The only randomized controlled trial (RCT) conducted with 25 patients with later life PD(A) showed that both alprazolam and imipramine were superior to a placebo (Sheikh & Swales, 1999). Unfortunately, for CBT no controlled comparisons are available. Another small-scale but uncontrolled trial with 20 elderly PD(A) patients suggested that CBT was efficacious (Swales, Solfvin & Sheikh, 1996) but, besides the study's uncontrolled nature and small sample size, interpretation of the results is also hampered by the high dropout rate (25%) and the lack of control for concurrent psychotropic drug use.

Despite the lack of evidence proving the efficacy of treatments of late-life PD(A), two recent meta-analyses of mixed patient groups suffering from later life anxiety disorders clearly showed both CBT and antidepressants to be effective (Hendriks et al., 2008a; Pinquart & Duberstein, 2007), with the Pinquart and Duberstein study showing

antidepressants to be more effective than CBT In younger and middle-aged adults, however, CBT was found to be more effective than antidepressants in the acute phase of PD(A) (Furukawa et al , 2006) Together, the results to date suggest a lower treatment efficacy for CBT relative to antidepressants in later life PD(A) Again, it needs to be noted that the majority of the available empirical and controlled studies was limited to generalized or mixed anxiety disorders while the few trials into PD comprised small numbers of patients

As far as we are aware, only one study directly compared CBT outcomes in younger and older patients with mixed anxiety disorders and depression (Walker and Clarke, 2001) showing similar effects in both age groups This study was, however, also limited by its small sample size (n = 32) as well as the heterogeneity of the patient group

Using a quasi-experimental design, in the current study we directly compare the effectiveness of CBT for PD(A) in younger and older patients The main objectives were 1) to examine the differential effects of manualized CBT for PD(A) as developed by Craske and Barlow (Craske & Barlow, 1993, Craske et al , 1994) in patients under and over the age of 60 years and 2) to examine age-related differences in feasibility as defined by dropout rates

6.2 Method

Design and patients

The present report describes an naturalistic, age-stratified treatment study of 172 patients diagnosed with PD(A) who were referred to our outpatient anxiety clinic (Forum GGz-Nijmegen, the Netherlands) Participants in the 18-to-60-year age bracket were recruited between January 1997 and December 2001 as part of a stepwise PD treatment study in which all patients first received protocolized CBT and, in case of non-response, subsequent random allocation to drug therapy (Kampman et al , 2002) All 60-plus participants were recruited between January 1999 and December 2005 as part of an RCT comparing protocolized CBT, paroxetine, and a waiting-list control condition (Hendriks, Keijsers, Kampman, Oude Voshaar, Verbraak, Broekman et al , submitted) Of this latter study, we included those clients that were directly randomly allocated to CBT and those that had been offered CBT because of an express preference The recruitment, assessment and treatment procedures were identical for both studies and performed by the same research group and psychotherapists (see below)

We approached all the participants whose diagnosis of PD(A) had been confirmed upon intake and who did not meet any of the studies' exclusion criteria, which were 1) severe somatic illnesses that could interfere with the CBT, 2) current use of an

antidepressant in an adequate dosage, 3) current and adequate psychological treatment, and 4) the presence of a primary psychiatric diagnosis of a psychotic, a bipolar, or a substance use disorder, and dementia. A comorbid diagnosis of other anxiety disorders, depression or dysthymia was allowed as long as PD(A) was the primary diagnosis. Those patients that consented to the present study received a baseline assessment in which the primary diagnosis of PD(A) was again confirmed using the Anxiety Disorders Interview Schedule-Revised (ADIS-IV; Bouman, et al., 1997; DiNardo et al., 1994), which was administered by independently trained assessors who were not involved in CBT delivery. Subsequently, the confirmed patients completed various questionnaires (see below), after which they started the 14-week treatment program. Following treatment completion they took an outcome assessment at week 15 using similar questionnaires.

6.3 Treatment protocol

Treatment was delivered individually and consisted of 14 weekly CBT sessions of fifty minutes each. Patients using benzodiazepines were tapered off before the start of the treatment under medical supervision or adhered to a fixed daily dose during the treatment.

The CBT was protocol-based and followed the Dutch version (Kampman & Keijsers, 1997) in accordance with the protocol of Craske and Barlow (1993) and compromised the following five components: 1) the provision of 'psycho-education' about panic, anxiety and avoidance behaviour, including the treatment rationale, 2) teaching relaxation techniques (applied relaxation), 3) interoceptive exposure, 4) cognitive therapy, and 5) exposure in vivo.

Therapists were experienced psychologists (MSc level) who had been extensively trained in the program Throughout the study period they were weekly supervised by senior therapists certified as supervisors by the Dutch Association for Behavioural and Cognitive Therapy to safeguard adequate application of the CBT techniques and adherence to the manual. Per session the therapists recorded which CBT components had been addressed and discussed these and any deviations from the manual with their supervisor. Adaptations to the intervention to meet a patient's specific circumstances were allowed if they were not in conflict with the manual.

6.4 Outcome measures

The primary outcome measure was PD(A) severity, defined as the extent of a patient's agoraphobic cognitions and agoraphobic avoidance. Agoraphobic avoidance was measured

with the Dutch version of the Mobility Inventory Avoidance scale (MI-A, Chambless et al , 1985) The MI-A has three subscales avoidance when alone (MI-AAL), avoidance when accompanied (MI-AAC), and frequency of panic attacks (MI-PF) The latter subscale offers a definition of panic attacks as formulated in the DSM-IV, after which the respondent is asked to indicate the number of actual panic attacks during the past seven days As the frequency of panic attacks is largely dependent on the level of agoraphobic avoidance and agoraphobic avoidance is a better predictor of treatment effects than the frequencies of panic attacks (De Beurs et al , 1995, Basoglu, Marks, Swinson, Noshirvani, O'Sullivan & Kuch, 1994b), we opted to use the total mean scores on the MI for our analyses (Kampman et al , 2002) The severity of agoraphobic cognitions was measured by the Dutch adaptation of the Agoraphobic Cognitions Questionnaire (ACQ, Chambless et al , 1984, De Beurs, 1993), a self-report questionnaire comprising 14 items to be rated on a 5-point scale The MI-A, the ACQ, and their Dutch adaptations are frequently used instruments in PD treatment outcome studies and have good test-retest reliability, high internal consistencies and reasonable concurrent validity (De Beurs, 1993, Chambless et al , 1984, Chambless et al , 1985)

Depressive symptoms and general psychopathology were evaluated as secondary outcome measures Depressive symptoms were assessed using the 20-item Beck Depression Inventory (BDI, Beck, 1988, Bouman, Luteijn & Albersnagel, 1985) The BDI has a sufficient and reasonable internal consistency and test-retest reliability and a good construct and discriminative validity General psychopathology was assessed with the 90-item Symptom Checklist (SCL-90), a self-report questionnaire divided into eight subscales (Derogatis et al , 1976, Arrindell & Ettema, 1986) The total sum score is a good reflection of the level of general psychopathological distress and as such included in our analyses The two scales and their Dutch adaptations are frequently used outcome measures and have good psychometric properties (Arrindell & Ettema, 1986, Beck & Steer, 1984, Beck, 1988, Bouman et al , 1985, Derogatis et al 1976)

The feasibility was evaluated by a proxy, namely the proportion of patients that withdrew during the 14-week treatment phase

6.5 Statistical analysis

Statistical differences between the two age groups at baseline were analyzed using chi-square tests or student *t*-tests To analyze treatment effects and potential between-group differences an overall 2 x 2 (Group < 60 years, ≥ 60 years x Time pre-treatment, post-treatment) MANOVA with repeated measures was performed for all outcome measures separately Dependent variables were agoraphobic avoidance (MI-A), agoraphobic cognitions (ACQ), general psychopathology (SCL-90), and depressive symptoms (BDI)

All analyses were corrected for gender, duration of illness and use of benzodiazepines and conducted both on a completer basis and an intent-to-treat basis, with the last observation carried forward (LOCF) in case of missing values at outcome, which latter analysis was considered to be the main analysis.

The SPSS 16.0 statistical analysis package was used (SPSS inc, 2008) Effects were tested two-sided and are reported as significant at a level of $p < .05$.

6.6 Results

Patient recruitment

A total of 208 patients received a diagnosis of PD(A), of which 189 gave their informed consent for participation. More specifically, in the 18-to-60 year age bracket 19 patients refused to participate, while all patients over 60 years consented to take part in the study. Two patients were subsequently excluded as their PDA diagnoses were not confirmed by the ADIS-IV (social phobia, $n = 1$; specific phobia, $n = 1$). As the ADIS-IV confirmed the diagnoses of PDA of all 60-plus patients, we excluded 15 of the younger patients with a diagnosis of panic disorder without agoraphobia to increase the comparability of the two age groups. The final study sample accordingly comprised 172 patients of whom 141 were under and 31 over 60 years of age.

Baseline comparison

Table 6-1 presents the demographic variables and diagnostic information for both age groups. The 60-plus patients were more frequently married or widowed ($\chi^2 = 47.4$, df = 3, $p < .001$) and had a lower prevalence of panic attacks in the week preceding the baseline test ($\chi^2 = 5.07$, df = 1, $p = .024$) compared to their younger counterparts.

Psychiatric comorbidity was common in both groups. In the under-60s group 46/141 (33%) patients were diagnosed with one ($n = 39$) or two ($n = 7$) comorbid disorders: 31 (22%) with an anxiety disorder, 14 (10%) with major depression or dysthymia, and 8 (6%) with a somatoform disorder. In the 60-plus group 7/31 (23%) patients were diagnosed with one ($n = 5$) or two ($n = 2$) comorbid disorders: 3 (10%) with an anxiety disorder, 2 (6%) with major depression or dysthymia, 2 (6%) patients with a somatoform disorder, and 2 (6%) other. The higher prevalence of comorbid anxiety disorders in the younger age group did not reach statistical significance ($\chi^2 = 2.43$, df = 1, $p = 0.12$) compared to the 60-plus patients and could be explained by the presence of 15 patients (11%) with a specific phobia, which phobias did not occur in the 60-plus group.

Table 6-1. Patient characteristics at baseline (n = 172) for the two age groups

Variables		Patients aged 18-60 years (n = 141)	Patients aged ≥60 years (n = 31)	Statistics
Age (yrs)	*M* (*SD*)	35 2 (10.3)	67.9 (5.0)	t = -17.2, df = 26.1, p < .001
Duration of anxiety (yrs)	*M* (*SD*)	7.8 (9.4)	12.0 (14.7)	t = -2.0, df = 35.6, p = .14
Female	*n* (%)	93 (66)	21 (68)	χ^2 = 0 85, df = 1, p = .84
Marital status:				
Married/living together	*n* (%)	66 (47)	21 (68)	χ^2 = 47.4, df = 3, p < 001
Divorced	*n* (%)	6 (4)	2 (7)	
Widow/widower	*n* (%)	0	7 (23)	
Never married	*n* (%)	69 (49)	1 (3)	
Living alone	*n* (%)	44 (31)	11 (36)	χ^2 = 0.21, df = 1, p = .64
Education				χ^2 = 3.52, df = 2, p = .17
Low	*n* (%)	40 (28)	14 (45)	
Medium	*n* (%)	53 (38)	10 (32)	
High	*n* (%)	48 (34)	7 (23)	
Panic attacks previous week	*n* (%)	102 (72)	16 (52)	χ^2 = 5.07, df = 1, p = .024
Benzodiazepines	*n* (%)	43 (31)	8 (26)	χ^2 = 0.27, df = 1, p = .61

Treatment feasibility

The overall dropout rate was 18% (n = 31). Twenty-nine patients in the under-60s group (21%) did not complete the full treatment, while only two 60-plus patients (7%) dropped out. Although dropout was substantially lower in the 60-plus group, the difference was not statistically significant (χ^2 = 3.43, df = 1, p = 0.06). Availability of post-treatment outcomes was related to dropout as all patients that withdrew from treatment (n = 31) also did not complete the post-treatment assessment, whereas in the completers (n = 141) only two patients did not take the final assessment (1%).

Treatment effects

Table 6-2 presents the means and standard deviations of all baseline and post-treatment outcome measures including the effect size expressed as Cohen's d values. The overall scores of the two groups differed both with respect to the ACQ (Completers: F = 19.5, df = 132,1, p < .001; LOCF: F = 24.2, df = 165,1, p < 001) and the BDI (Completers: F = 27.5, df = 133,1, p < .001; LOCF: F = 32.6, df = 166,1, p < .001), with significantly lower pre- and post-treatment scores on the ACQ and higher scores on the BDI for the older patients.

The MI-A agoraphobic avoidance scores yielded a significant main effect of Time (Completers: F = 8.80, df = 133,1, p = .004; LOCF: F = 6.27, df = 166,1, p = .013) indicating improvement at follow-up in both age groups. This effect was significantly larger for the 60-plus group as is reflected in the significant Time by Age interaction (Completers:

Table 6-2. Pre- and post-treatment outcomes and effect sizes for the two age groups

Condition	Pre-treatment Mean (*SD*)	Post-treatment Mean (*SD*)		Cohen's *d*	
		Completers	LOCF	Completers	LOCF
Patients aged <60 years (n = 141)					
ACQ	2.2 (0 6)	1.9 (0 6)	1 9 (0.6)	0.5	0.5
MI-A	2.5 (0.8)	2.0 (0.8)	2.1 (0.8)	0.6	0 5
SCL-90	184.6 (49.3)	147.7 (40.4)	156.3 (44.3)	0.8	0.6
BDI	13.5 (7.6)	8.7 (6.2)	9.7 (7.0)	0.7	0.5
Patients aged ≥60 years (n = 31)					
ACQ	1.6 (0.5)	1.4 (0.4)	1.4 (0.4)	0.4	0.4
MI-A	2.5 (1.0)	1.8 (0.9)	1 8 (0.8)	0 7	0.8
SCL-90	167.4 (48.0)	142.0 (33.0)	142 3 (31.4)	0.6	0.6
BDI	13.1 (8.9)	10.2 (7 1)	10 3 (7.0)	0.4	0.3

Abbreviations: ACQ = Agoraphobic Cognitions Questionnaire, BDI = Beck Depression Inventory, LOCF = Last Observation Carried Forward, MI-A = Mobility Inventory Avoidance scale, SCL-90 = Symptom Checklist.

F = 4.86, df = 133,1, p = .029; LOCF: F = (166,1), df = 166,1, p = .006).

For the other primary outcome parameter, ACQ agoraphobic cognitions, time effects achieved significance in the completers analyses, but not in the LOCF analyses (Completers: F = 4.33, df = 132,1, p = .039; LOCF: F = 3.54; df = 165,1, p = .062). Similar results were found for the secondary outcome measures BDI depressive symptoms (Completers: F = 4.86, df = 132,1, p = .03; LOCF: F = 2.78, df = 167,1, p = .10) and SCL-90 general psychopathology (Completers: F = 6.51; df = 126,1; p = 012; LOCF· F = 3.32, df = 167,1, p = .07). In none of these analyses significant interactions with age were found (range p-values .15 through .78) Taken together, the results demonstrate that CBT had significantly improved all outcomes in both age groups with a larger improvement in agoraphobic avoidance in the 60-plus group compared to the younger patients.

The post-treatment panic-free ratio for the completers was 69% for both age groups (< 60s: n = 96; ≥ 60s: n = 20), with the LOCF yielding ratios of 62% (n = 87) and 71% (n = 22), respectively.

6.7 Discussion

Main findings

Although originally developed for and extensively tested in younger to middle-aged adults with panic disorder, the protocolized CBT we delivered in our study was effective in improving avoidance behaviour and anxiety cognitions in both the younger and the older participants with PDA. The intervention even resulted in a significantly stronger

reduction of avoidance behaviour in the 60-plus group. In contrast to what has frequently been suggested in the literature, we found our protocol to be as feasible in older patients as it was in younger patients, with a trend towards superior feasibility in the older patients

Comparison with the literature

Baseline differences – Agoraphobic cognitions were significantly less severe and panic attacks in the week before treatment less frequent in our 60-plus patients than they were in their younger counterparts. Agoraphobic avoidance, the most important measure of disease severity, however, did not differ between the two age groups In contrast to our expectations, the duration of illness also failed to show any age-related differences. In line with previous empirical findings the prevalence of benzodiazepine usage did not differ between the under- and the over-60s patients (Benitez, Smith, Vasile, Rende, Edelen & Keller, 2008).

Treatment effects – An important finding was the remarkably low dropout rate in the over-60s group: 6% versus 22% in the younger adults. Although the difference was statistically not significant, the ratio is indicative of how well our elderly patients tolerated the demanding and challenging aspects of the targeted CBT (e.g. the daily homework assignments and exposure exercises). We had decided not to make age-specific adaptations to the treatment protocol because this could have affected the comparability of the treatment results of our two age groups. Although some small-scale studies did indicate that such modifications enhanced the efficacy of CBT for late-life generalized anxiety disorder (GAD) (Mohlman et al., 2003; Stanley et al., 2003b) these findings are preliminary. The comprehensive and methodologically more sophisticated study by Stanley et al. (2003a) showed comparable effect sizes as in CBT for younger adults with GAD.

The effect sizes of the primary outcome measures ranged between 0.4 and 0.8, indicating moderate to large effects in both age groups, which is comparable to the effect sizes reported in recent meta-analytic reviews of PD-specific CBT for adult patients (Haby et al., 2006) and for CBT for GAD in older people (Pinquart & Duberstein, 2007). Major risk factors of later life anxiety disorders are increasing social deprivation and isolation, which are key determinants of the quality of life in elderly people (Beekman et al., 2000) The large effect size (0.8) found for avoidance behaviour in our 60-plus group indicates that targeted CBT helps secure a better quality of life for this older patient group by substantially lowering these risks.

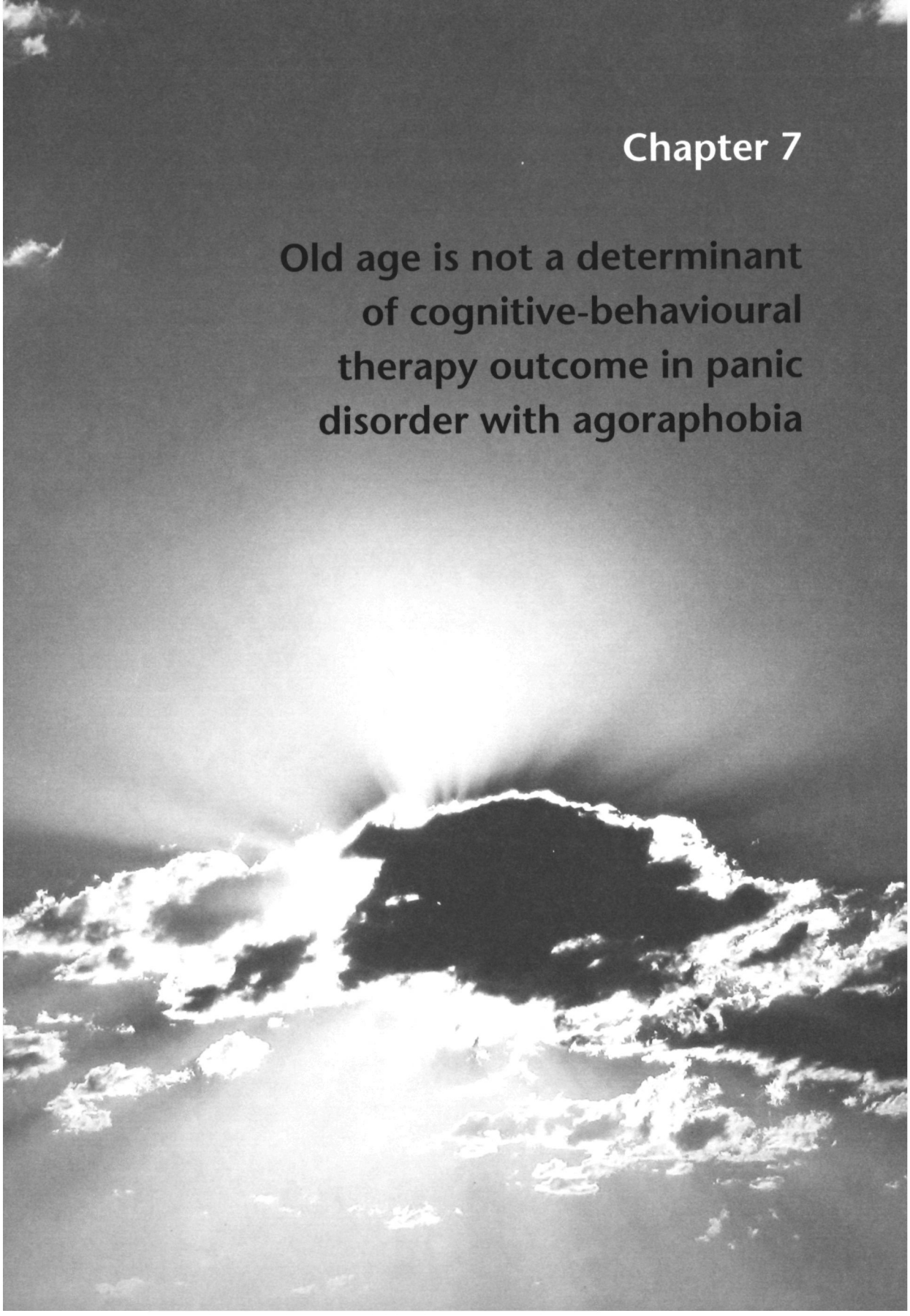
Strengths and limitations

For a proper interpretation of the current results some limitations should be taken into account. First, the size of our 60-plus sample was relatively small, although this was to be expected as PD(A) in later life tends to go largely un(der)diagnosed and un(der) treated (De Beurs et al., 1999). The average age in our over-60s group was 68 years, but, although not statistically significant, post-hoc analyses were suggestive of even better effects in the patients aged over 70 years.

Secondly, we used self-report instruments to evaluate treatment outcome. Although studies validating self-report anxiety inventories originally developed for younger adults (18-65 yrs) in our age group are scarce, the available studies found no major objections for their use in older populations (Fuentes & Cox, 2000; Goldberg et al., 2003; Mohlman, de Jesus, Gorenstein, Kleber, Gorman & Papp, 2004; Crittendon & Hopko, 2006). The only study directly comparing the ACQ between older and younger PD patients found, similar to our results, lower scores for the older patients (Sheikh et al., 2004a). Furthermore, earlier findings of self-assessed anxiety cognitions in younger adults were inconsistent. The ACQ may thus not be the most suitable instrument to establish the scope of anxiety cognitions in PD(A) (Khawaja, 2003). The use of observer-rated instruments like the Panic Disorder Severity Scale (PDSS; Shear et al., 2001) or the Panic Agoraphobia Scale (PAS; Bandelow et al., 2000), might have been more suitable but neither were available in Dutch translation nor psychometrically tested at the launch of our project.

6.8 Final conclusion

Given the 2% prevalence of late-life (agoraphobic) panic disorder and its underdiagnosis and undertreatment, we need to educate both general practitioners and the elderly themselves in recognizing anxiety symptoms. Acknowledging the preference of older people for CBT over drug therapy (Wetherell et al., 2004b), the associated side effects of drug therapies (Ensrud et al., 2002; Ensrud et al., 2003; French et al., 2006; Hartikainen et al.; 2007) and the similar effect sizes that have been obtained for CBT and antidepressants for anxiety disorders in general in this age group (Pinquart & Duberstein, 2007), CBT is a good treatment alternative and should be made more widely available for elderly patients suffering from panic disorder. Future studies should then expand our knowledge of existing CBT approaches and the potential of age-related modifications.



Chapter 7

Old age is not a determinant of cognitive-behavioural therapy outcome in panic disorder with agoraphobia

This chapter has been submitted for publication:

Hendriks, G.J., Keijsers, G.P.J., Kampman, M., Broekman, T.G., Oude Voshaar, R.C. & Hoogduin, C.A L. Old age is not a determinant of cognitive-behavioural therapy outcome in panic disorder with agoraphobia.

7.1 Introduction

A systematic review and meta-analysis showed that in the acute-phase treatment of panic disorder with agoraphobia (PDA) cognitive behavioural therapy (CBT) is more effective compared to antidepressants, whereas the combination of both treatments is most efficacious in the short term. Since CBT alone and the combined treatments are equally effective in the long term, both are considered first-line treatments for PDA (Furukawa et al., 2006).

In elderly patients suffering from anxiety disorders it is suggested that drug treatment might be preferable over CBT (Pinquart & Duberstein, 2007) However, the empirical ground for the preference of drug treatment over psychological treatment for elderly patients with PD(A) is small. One randomized controlled trial (n = 25) showed superiority of alprazolam and imipramine over placebo treatment in late-life PD(A) (Sheikh & Swales, 1999). Furthermore, two case series have suggested efficacy for both CBT (N = 20) and sertraline (N = 10) in the treatment of late-life PD(A) (Sheikh et al., 2004a; Swales et al., 1996). There was only one study directly comparing CBT and drug therapy in elderly patients in mixed population of anxiety disorders. This study showed superiority of drug treatment over CBT (Schuurmans et al., 2006). However, it is questionable wether the findings of this study pertain to panic disorder patients. Only 45% of the patients suffered from PD, and 32% of the patients dropped out prematurely from the study.

Recently, we concluded a RCT (N = 49) in which both paroxetine and CBT were superior to a waiting-list control condition in late-life PD(A). No differences in outcome were observed between CBT and paroxetine treated patients (Hendriks et al., submitted).

As substantial evidence support CBT for PD(A) as a first-line treatment in adult life, it is relevant to study age-related variables in the outcome of CBT in a sample including a sufficiently large number of elderly patients.

Research into predictors of outcome in PD(A) in young and middle-aged adults showed only initial severity of symptoms as a consistent predictor of outcome (Kampman, Keijsers, Hoogduin & Hendriks, 2008). A number of studies found a negative effect of older age, earlier age at onset and longer duration of illness on outcome (DOI) of CBT for PD(A) (Basoglu et al., 1994b; De Beurs et al., 1995; Dow, Kenardy, Johnston, Newman, Taylor & Thomson, 2007a; Dow, Kenardy, Johnston, Newman, Taylor & Thomson, 2007b). However, these findings were limited to young and middle-aged patients and their findings cannot readily be generalized to elderly patients. Studies in outcome prediction in elderly patients with anxiety disorders are lacking. In fact, only Wetherell and colleagues (2005b) studied predictors of outcome in late-life anxiety. They found in an elderly population with generalized anxiety disorder, as was shown in young and middle-aged adults with PD(A) also (Kampman et al., 2008), that initial severity of symptoms was related to outcome.

The current study was set up to examine a widespread view among general practitioners and mental health professionals that old age and a long DOI is negatively associated with outcome in the treatment of anxiety disorders in later life (Stanley & Averill, 1999) We were especially interested in PDA as epidemiological evidence showed PDA as clinically more severe and more in need for treatment compared to PD without agoraphobia (Grant et al , 2006) The specific effect of (very) late-onset of PDA remains unknown, although it has been suggested that an onset at older age results in less severe symptoms (Segui et al , 2000, Sheikh et al , 2004a) as compared to an onset earlier in life, and from previous prediction studies it can be concluded that lower symptom severity is related to better treatment outcomes (Kampman et al , 2008)

The effect of age, age at onset and DOI on CBT outcome for PDA with respect to both agoraphobic cognitions and agoraphobic avoidance over a broad age span is examined We hypothesize that after correction for initial symptom severity 1) age is not related to outcome and 2) a longer DOI predicts a less favourable outcome Due to the lack of empirical data, we do not have an a priori hypothesis on the effect of age at onset of the PDA

7.2 Method

Design and patients

A naturalistic treatment study of patients suffering from PDA who were referred to a specialized outpatient anxiety clinic was conducted from January 1997 through December 2005 As the treatment program was opened for the elderly since January 1999, older patients suffering from anxiety disorders were also referred All patients who were diagnosed with a PDA during intake and did not meet the exclusion criteria, were asked to participate in the study and were invited for a baseline assessment Exclusion criteria were 1) a severe somatic illness interfering with appropriate application of CBT, 2) current use of an antidepressant in an adequate dosage, 3) current and adequate psychological treatment, and finally 4) presence of a primary psychiatric diagnosis of a psychotic disorder, bipolar disorder, substance use disorder or dementia A comorbid diagnosis of other anxiety disorders, depression or dysthymia was allowed as long as PD(A) was the primary and targeted diagnosis

Those patients who consented to the present study received a baseline assessment in which a primary diagnosis of a PDA had to be confirmed by the Dutch version (Bouman, et al , 1997) of the Anxiety Disorders Interview Schedule-Revised (ADIS-IV, DiNardo et al , 1994) The ADIS-IV was administered by independent and trained assessors who were not involved with treatment delivery Subsequently, several self-report instruments had to be completed (see below) After the baseline assessment, patients directly started

the 14-week treatment programme. After concluding this programme, an outcome assessment was conducted (week 15) using similar questionnaires.

Treatment protocol

The cognitive-behavioural treatment programme (CBT) was delivered individually and consisted of 14 weekly sessions of fifty minutes each. The CBT was manual-based, followed the Dutch version (Kampman & Keijsers, 1997) of the manual of Craske and Barlow (1993), and comprised the five following components: 1) provision of psycho-education about panic, anxiety and agoraphobic avoidance, including the treatment rationale, 2) teaching relaxation techniques (applied relaxation), 3) interoceptive exposure, 4) cognitive therapy, and 5) exposure in vivo.

The treatment was delivered by psychologists (MSc level) experienced and extensively trained in the manuals. Throughout the study period therapists were weekly supervised by cognitive-behavioural therapists certified as supervisors for the Dutch Association for Behavioural and Cognitive Therapy to safeguard adequate application of the CBT techniques and adherence to the manual For this purpose, therapists had to record which CBT components had been addressed within each session, which was discussed with the supervisor. Deviations from the treatment manual were discussed. Adaptations to the intervention to meet a patient's specific circumstances were allowed if they were not in conflict with the manual.

Patients using benzodiazepines were tapered off before the start of the study under medical supervision or had to adhere to a fixed daily dose during CBT. The use of benzodiazepines as needed was not allowed.

Dependent variables

The primary outcome measure was panic disorder severity, defined as the severity of agoraphobic avoidance and the severity of agoraphobic cognitions after treatment.

Agoraphobic avoidance was measured by the Mobility Inventory Avoidance scale (MI-A) (Chambless et al., 1985) The MI-A contains 3 subscales: avoidance when alone (MI-AAL), avoidance when accompanied (MI-AAC), and frequency of panic attacks (MI-PF). The MI-PF offers a definition of panic attacks as formulated in the DSM-IV, after which the respondent is asked to indicate the number of actual panic attacks during the past 7 days. As the panic attack frequency is largely dependent on the level of the agoraphobic avoidance and agoraphobic avoidance is a better predictor of treatment effects than the panic attack frequency (Basoglu et al., 1993; De Beurs et al., 1994), the total mean scores on the MI-A at end of treatment will be used in the analyses (Kampman et al., 2002).

The severity of agoraphobic cognitions was measured by the Agoraphobic Cognitions Questionnaire (ACQ) (Chambless et al., 1984; De Beurs, 1993) The ACQ is a self-report

questionnaire containing 14 items that had to be rated on a 5-point rating scale. The sum score at end of treatment will be used in the analyses.

The ACQ, the MI-A, and their Dutch adaptations are frequently used instruments in panic disorder treatment outcome studies and have good test-retest reliability, high internal consistencies and reasonable concurrent validity (Chambless et al., 1984; Chambless et al., 1985; De Beurs, 1993).

Independent variables

The independent variables under study were age of the participants, age of onset of the panic disorder (defined as the self-report age of the first panic attack based on the ADIS-IV interview) and DOI (defined as the actual age minus the age of onset).

Late-onset panic disorder was defined as an age of onset after the age of 60 years, similar to Segui and colleagues (2000) and similar to the definition of late-onset mood disorders (Alexopoulos, Young & Meyers, 1993; Reynolds III, Dew, Frank, Begley, Miller, Cornes et al., 1998).

Covariates

Some covariates may be important in comparing outcome in CBT between younger and older adults First, sociodemographic variables are different between younger and older adults, e.g marital status or educational level, and may be related to outcome in both the pharmacological and psychological treatment of affective disorders (Schoevers & Dekker, 2008). Furthermore, although depression in young and middle-aged adults is inconsistently related to outcome in CBT for PD(A) (Kampman et al., 2008), in elderly with anxiety disorders and comorbid depression treatment outcome may be poorer (Lenze, Mulsant, Shear, Alexopoulos, Frank & Reynolds, 2001). Additonally, insomnia is a relevant stressor in elderly and is associated with anxiety disorders in later life (Hidalgo, Gras, Garcia, Lapeira, del Campo & Verdejo, 2007). Therefore, sociodemographic variables, severity of depressive symptoms and sleeping problems were considered potential confounders. All sociodemographic variables were entered as dichotomous variables: currently married (yes/no), living alone versus with others, and higher eduction, i.e. a minimal educational level at a bachelors degree (yes/no). The severity of depressive symptoms at baseline was assessed with the Beck Depression Inventory (BDI); a 20-item, self-reported questionnaire (Beck, 1988; Bouman et al., 1985). The BDI has a sufficient and reasonable internal consistency and test-retest reliability and a good construct and discriminative validity. The severity of sleeping complaints was assessed with a subscale of the Symptom Checklist (SCL-90), a 90-item self-report questionnaire containing 8 subscales (Arrindell & Ettema, 1986; Derogatis et al., 1976). Both scales, the BDI and the SCL-90, do have Dutch versions with good psychometric properties (Arrindell & Ettema, 1986; Beck, 1988; Bouman et al., 1985; Derogatis et al., 1976).

Statistical analyses

Multiple linear regression analyses were applied separately for each of the dependent variables, i.e. agoraphobic avoidance and agoraphobic cognitions. Each independent variable of interest (age, age of onset, DOI) was separately tested after having been corrected for the baseline level of agoraphobic avoidance and agoraphobic cognitions, respectively. A similar procedure was conducted for each of the covariates of interest. When a covariate was related to the primary outcome of interest at $p < .15$, the covariate was added as predictor to the regression model to check for potential confounding effects.

The DOI had a skewed distribution, which normalized after log transformation. For the sake of interpretation, the non-transformed values will be mentioned in the text, but all statistics will be based on the log-transformed values. All other variables were either normally distributed or dichotomous.

The SPSS 16.0 statistical analysis package was used (SPSS inc, 2008). Effects were tested two-sided and are reported as significant at a level of $p < .05$.

7.3 Results

Patient recruitment

A total of 208 patients received a diagnosis of a panic disorder, of which 189 gave informed consent. A further total of 17 patients were excluded as the diagnosis of PDA was not confirmed using the ADIS-IV (panic disorder without agoraphobia, $N = 15$; social phobia, $N = 1$; specific phobia, $N = 1$). The final study sample comprised 172 patients: 141 patients were aged between 18 and 60 years and 31 patients were aged over 60 years

The age of onset differed significantly between elderly and younger patients: 56 (*SD* 15) versus 27 (*SD* 10) years ($p < .001$). The DOI was not significantly different between adult and elderly patients: 7.8 (*SD* 9.4) versus 12.0 (*SD* 14.7) years ($p = .68$). Among elderly patients (> 60 years), those with a late-onset panic disorder had a significantly shorter DOI: 3.2 (*SD* = 3.2) versus 24.1 (*SD* = 15.9) years ($p < .001$).

Agoraphobic avoidance

Table of 7-1 presents analyses of agoraphobic avoidance. As expected, the best predictor agoraphobic avoidance severity at end of treatment was baseline severity of agoraphobic avoidance. As a continuous variable, age was not significantly related to treatment outcome. However, when split up in adult and elderly patients, elderly patients had significantly better results. Furthermore, within the subgroup of elderly patients, a higher age turned out to be associated not with less favourable outcome but with more favourable outcomes. Similarly, a higher age of onset and shorter DOI were related to a better outcome in the elderly patient group.

Table 7-1. Regression of each variable of interest on agoraphobic avoidance at end of treatment in a separate model

	Whole sample (n = 148)			Under 60 (n = 119)			Over 60 (n = 29)		
Variables	R^2	β	p	R^2	β	p	R^2	β	p
Agoraphobic avoidance at baseline	.50	.71	<.001	.54	.73	<.001	.44	.67	<.001
Age (continuous)[a]	.51	- 09	.15	.56	07	.33	.53	-.30	.037
Age dichotomized at 60[a]	.52	- 13	032	-	-	-	-	-	-
Age of onset (continuous)[a]	.52	-.13	030	.56	.08	21	.60	-.40	.003
Late-onset panic disorder[a]	.56	-.23	<.001	-	-	-	.62	-.43	.002
Duration of illness (log-transformed)	.51	.09	.14	.54	.02	73	.53	.30	.038

a Univariate analyses, adjusted for level of avoidance at baseline.

In elderly patients, both, age and DOI, were independently associated with treatment outcome in one overall regression model (effect of age, β = -.30, p = .024; effect of DOI, β = .31, p = .025) (Model R^2 = .62).

Late-onset panic disorder and DOI cannot be included in one regression analysis as both variables are intrinsically related or, in other words, a late-onset implies a short duration. For this reason, we repeated the analysis with a restriction to those patients with a DOI of less than 5 years. This analysis revealed significantly better outcomes for patients with a late-onset panic disorder: whole sample (β = -.22, p = .015, model R^2 = .46), elderly subgroup (β = -.61, p = .044; model R^2 = .39). Restricting our sample to those with a DOI of less than 2 years, still yielded a significant superior effect for late-onset panic disorder (whole sample, β = -.34, p = .005, model R^2 = .46; elderly patients, β = -.84, p = .003, model R^2 = 74).

Sleeping problems as assessed with the SCL-90 was the only covariate associated with outcome in the whole sample and younger age sample. Adding this variable to the final regression models did not change outcome (data not shown).

Anxiety cognitions

Table 7-2 presents similar analyses for anxiety cognitions. In this case, we found no effect of age on therapy outcome Again, a shorter DOI was related to a better outcome, whereas a higher age of onset was only related to a better outcome among the elderly patients. Repeating the analyses for late-onset panic disorder with a restriction to those patients with a short DOI, however, did not yield significant better effects for late-onset panic disorder anymore (data not shown).

Marital status was the only covariate associated with outcome in the whole sample. Adding this variable to the final regression models did not change outcome (data not shown).

Table 7-2. Regression of each variable of interest on anxiety cognitions at end of treatment in a separate model

	Whole sample (n = 148)			Under 60 (n = 119)			Over 60 (n = 29)		
Variables	R^2	β	p	R^2	β	p	R^2	β	p
Anxiety cognitions at baseline	.39	.63	<.001	.33	.57	<.001	.48	.69	<.001
Age (continuous)[b]	41	.04	.55	35	.10	.22	.48	.03	.86
Age dichotomized at 60[b]	.39	-.03	.69	-	-	-	-	-	-
Age of onset (continuous)[b]	.41	-.04	.59	.34	.05	.58	.62	-.41	.006
Age of onset (< > 60 years)[b]	41	-.07	.33	-	-	-	.54	-.25	.085
Duration of illness (log-transformed)[b]	.41	.14	.039	.34	.10	.19	.60	34	.012

b Univariate analyses, adjusted for level of anxiety cognitions at baseline.

7.4 Discussion

Confirming the results of previous studies by demonstrating a worse treatment effect in the most severely ill patients, the main finding of our study is that a higher age and a higher age of onset were not associated with a negative treatment outcome. In contrast, both, a higher age and a higher age of onset, predicted even better treatment effects with respect to the level of agoraphobic avoidance, whereas these variables were only marginally related to treatment effects on the level of anxiety cognitions.

Effect of age

Conform our hypothesis, age was not a predictor for CBT outcome. However, in the subsample of elderly patients, higher age was associated with a larger reduction of agoraphobic avoidance (but not anxiety cognitions). These findings contrast with several previous studies showing a lower than expected effect size of protocolized CBT in elderly patients with anxiety disorders compared to effect sizes of CBT in younger adults (Schuurmans et al., 2006). The difference may be contributed to the variability in underlying psychiatric diseases in the Schuurmans study (2006), which included patients with generalized anxiety disorder, panic disorder and agoraphobia without panic disorder. If true, our findings suggest that disorder-specific treatment protocols should also be preferred in elderly patients similar to the application of CBT in younger and middle-aged adults.

Effect of age of onset

With respect to the improvement of agoraphobic avoidance, a higher age of onset was associated with a better outcome, which was most pronounced in the elderly subgroup. The effect of age of onset was not related to improvement of anxiety cognitions in the whole

sample, but in the elderly subgroup it was still associated with a stronger improvement of anxiety cognitions. The more favourable prognosis of late-onset PDA is in line with findings that the late-onset type of PDA is a milder form (Segui et al., 2000; Sheikh et al., 2004a). Large epidemiological projects showed that only 5% of the patients with panic disorder had an age of onset after the age of 56 years and 1% after the age of 63 years (Kessler et al., 2005a). This low incidence rate might be explained by methodological limitation of epidemiological studies as well as a referral bias for treatment in clinical practice. Irrespective of the explanation, in old age psychiatry patients with late-onset PDA constitute approximately half of the patients with PDA under treatment as found in our study (18/31, 68%) and those of others (Segui et al., 2000), which justifies special attention to this specific group of patients.

Effect of duration of illness

A longer DOI was associated with a negative treatment outcome, which is in line with most previous studies (Basoglu et al., 1994b; De Beurs et al., 1995). For clinicians, such findings may lead to the conclusion that elderly patients do have a worse prognosis when entering treatment. In our study, however, even after correction for DOI, a higher age of the participants remained associated with a significantly better treatment outcome with respect to the severity of agoraphobic avoidance.

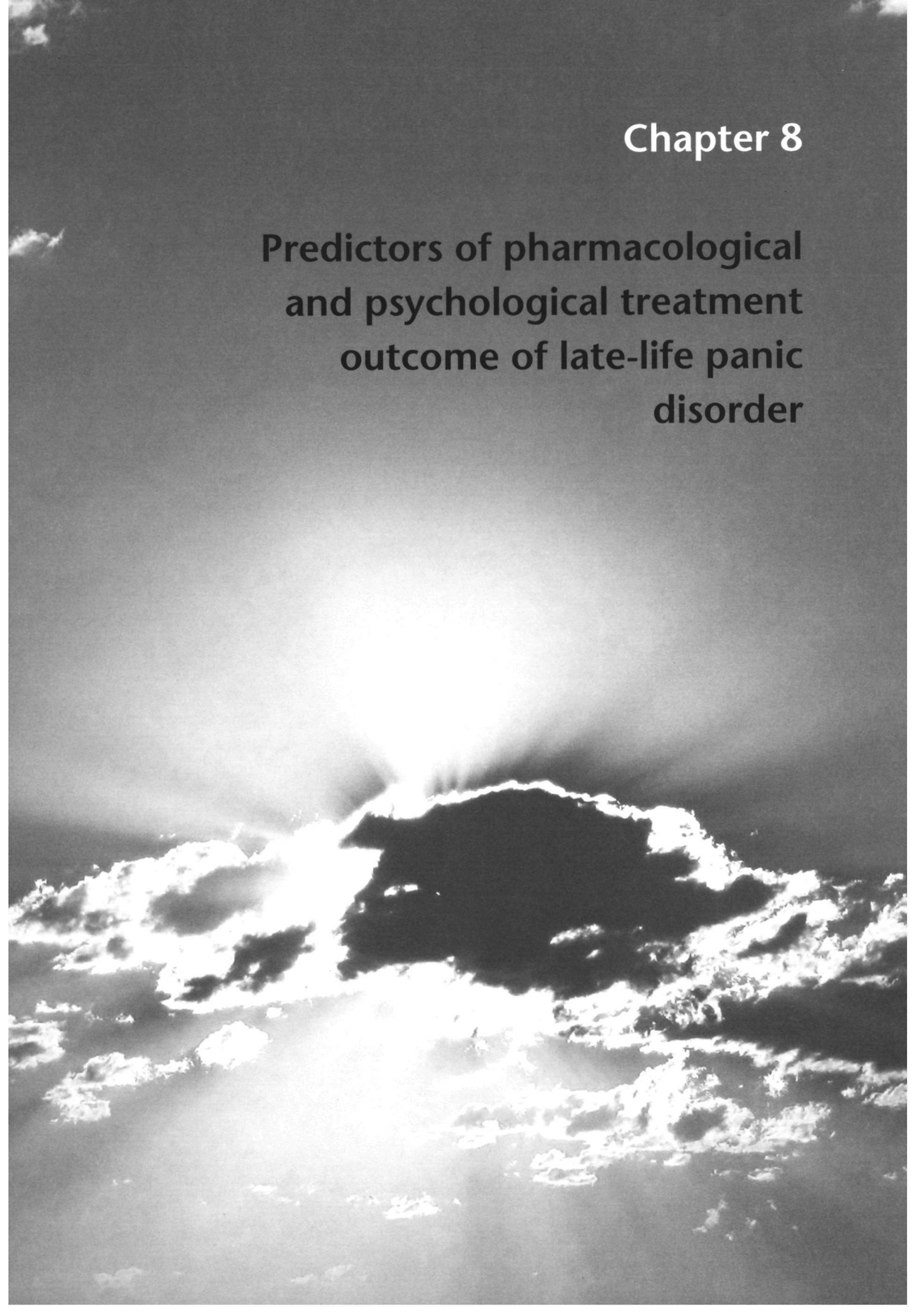
Strengths and weaknesses

For a good interpretation of the present findings, some limitations should be acknowledged. First, considerable debate exists on the definition of late-onset panic disorder with a range between 30 and 50 years (Katerndahl & Talamantes, 2000; Sheikh et al., 2004a). The median age of onset of panic disorder in large epidemiological projects is 25 years (Kessler et al., 2005a). These definitions, however, largely neglect the effects of ageing on the symptomatology and severity of the panic disorder. It has been shown that the symptom severity of panic disorder as measured with self-report questionnaires decreases with age (Sheikh et al., 2004a), as well as physiological arousal in panic challenge studies (Flint et al., 1998; Griez et al., 2007). It is unknown to what extent these findings can be translated to a lower severity of the panic disorder in later life per se. In our study only 2 patients aged above 60 years had an onset before the age of 25 years. For this reason, it was not possible to examine this definition of a late-onset in our sample and we have chosen a clinical definition of late-onset at 60 years, in line with Segui and colleagues (2000). Secondly, although the age of onset and DOI are based upon data gathered within a well-validated structured interview (ADIS-IV), these data are retrospectively collected. However, it was found that within a time period of four years test-retest reliability of the recall of age at onset for panic disorder was good (Prusoff, Merikangas & Weissman, 1988). Thirdly, we used self-report instruments to evaluate

treatment outcome and did not use a clinical global impression scale or the ADIS-IV interview at outcome Although validation studies of self-report anxiety questionnaires in older patients are scarce, the available studies did not find major objections for their use in older populations (Crittendon & Hopko, 2006, Fuentes & Cox, 2000, Goldberg et al , 2003)

Clinical implications / final conclusion

Our results clearly show that high age should not be an exclusion criterion for CBT and even in the older age groups (> 60 years) shows better results compared to younger patients



Chapter 8

Predictors of pharmacological and psychological treatment outcome of late-life panic disorder

This chapter has been submitted for publication:

Hendriks G.J , Keijsers G P J , Kampman M , Oude Voshaar R.C & Hoogduin, C.A L. Predictors of pharmacological and psychological treatment outcome of late-life panic disorder.

8.1 Introduction

Old age is often seen as a negative predictor of treatment outcome in panic disorder with or without agoraphobia (PD(A)), just as it is in late-life anxiety and depression (Mitchell & Subramaniam, 2005). Empirical studies, however, only point to the severity of the initial symptoms as a consistent predictor of therapy outcome in PD(A) (Kampman et al., 2008), although the findings are exclusively based on younger and middle-aged populations, which limits their generalization to later life. Furthermore, interpretation of the results of late(r)-life studies can be complicated due to the sample heterogeneity caused by large differences in the age of disease onset Epidemiological surveys show that with a median age of onset of 25 years, most patients with late-life PD(A) have been suffering from the effects of their condition for quite some time (Kessler et al., 2005a). Nevertheless, a substantial number of elderly patients is referred on account of a (very) late-onset type of PD(A), having had their first symptoms as late as in their sixties (Segui et al., 2000). One may hypothesize that especially this late-onset type is more susceptible to CBT than the early-onset type with its consequential lengthy illness duration.

The current study evaluated whether age, age at onset, and duration of illness (DOI) have any differential effects on the outcome of pharmacological and psychological treatment approaches for agoraphobic PD in elderly patients.

8.2 Methods

A total of 49 patients aged 60 years and over diagnosed with PDA, as confirmed by the Dutch version (Bouman et al., 1997) of the Anxiety Disorders Interview Schedule for DSM-IV (ADIS-IV, DiNardo, 1994), were randomly allocated to three study conditions: 40 mg/d paroxetine (n = 17), cognitive-behavioural therapy (CBT; n = 20), or a standard waiting-list control condition (n = 12). A detailed description of the interventions and the baseline and end-of-treatment interview assessments is given elsewhere (Chapter 4, this thesis).

In this brief report we describe the results of multiple regression analyses predicting post-treatment effects on agoraphobic avoidance and agoraphobic cognitions in the paroxetine and the CBT condition separately in terms of the total scores on the Mobility Inventory Avoidance scale (MI-A; Chambless et al., 1985) and the total scores on the Agoraphobic Cognitions Questionnaire (ACQ; Chambless et al., 1984), respectively. Both questionnaires are frequently used in PD(A) treatment outcome studies and for both Dutch versions are available with proven good psychometric properties (De Beurs, 1993).

Participants' age, age at PDA onset, defined as the participant's age at the time of the first panic attack as reported during the ADIS-IV interview, and DOI defined as the actual age minus the age at onset, were regressed on the MI-A and ACQ sum scores,

respectively. The treatment conditions were examined separately by multiple regression analyses after controlling for baseline symptom severity. When the treatment arms yielded different predictors, the modalities were examined in one model.

8.3 Results

Outcome data were available for 14/17 (82%) patients assigned to the paroxetine condition and for 18/20 (90%) in the CBT condition The patients' baseline characteristics did not differ across conditions: they were on average 69 2 (*SD* = 4.7) years old and 57% were women; the mean baseline MI-A score was 2.4 (*SD* = 0.9) and the mean baseline ACQ score 1.7 (*SD* = 0.5). Post-treatment mean MI-A and ACQ scores were respectively 1.8 (*SD* = 0 9) and 1.4 (*SD* = 0.4) (see Chapter 4, this thesis).

The results of the multiple regression analyses are reported in Table 8-1. Late-onset type and a shorter DOI predicted significantly better outcome with respect to both agoraphobic cognitions and avoidance behaviour in the CBT condition. However, when both treatment conditions were entered into one regression model, only the late-onset PDA (Late-onset type by Condition: R^2 = .50, β = -1.80, *p* = 009) yielded a significant interaction term with treatment condition in favour of CBT, whereas interaction of treatment condition with DOI did not reach significance (DOI by Condition: R^2 = .49, β = .54, *p* = .10). With respect to avoidance behaviour, neither DOI nor late-onset type yielded a significant interaction term with treatment condition (DOI by Condition: R^2 = .55, β = -.56, *p* = .22; Late-onset type by Condition: R^2 = .62, β = .06, *p* = .07).

Table 8-1. Results of the multiple regression analyses testing the predictive values of three variables of interest on treatment outcome after controlling for baseline symptom severity

	Paroxetine condition (*n* = 17)						CBT condition (*n* = 20)					
	MI-A			ACQ			MI-A			ACQ		
	R^2	β	*p*	R^2	β	*p*	R^2	β	*p*	R^2	β	*p*
Age*	.68	.13	.53	.22	.29	.30	41	-.25	.24	.47	.13	.49
Late-onset PDA (yes/no)*	.68	-.11	.54	.26	-.48	11	.60	-.51	.007	.61	.40	.025
Duration of illness* #	68	.11	.53	.14	.08	.78	.50	.39	.052	.68	48	.005

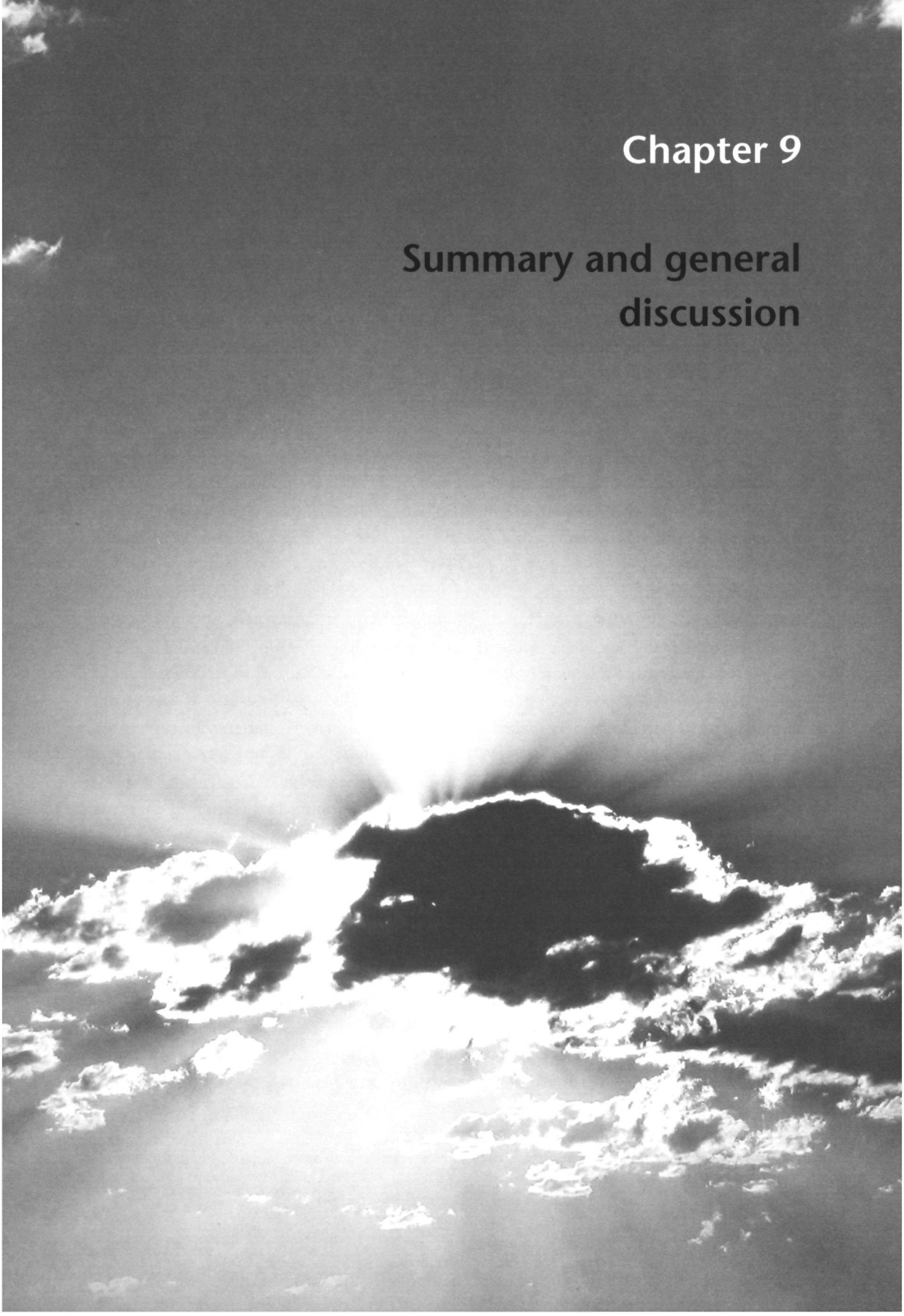
* Regression analyses with post-treatment MI-A and ACQ total scores as the dependent variables corrected for baseline MI-A and ACQ scores, respectively

\# Due to a skewed distribution the analyses are based on the log-transformed values.

Abbreviations ACQ = Agoraphobic Cognitions Questionnaire, MI-A = Mobility Inventory Avoidance scale, CBT = Cognitive-Behavioural Therapy, PDA = Panic Disorder with Agoraphobia

8.4 Discussion

Although preliminary because of the small sample size, this first randomized controlled treatment study of agoraphobic panic disorder in later life revealed some interesting findings. In contrast to what is generally assumed in clinical practice, with our study we showed that age is not related to treatment outcome. Interestingly, we did find differential effects for paroxetine and CBT for the other predictors tested. those patients with late-onset PDA and shorter illness duration had a more favourable outcome following CBT. No such effects were observed in the paroxetine condition. These findings suggest that CBT may be treatment of choice for the late-onset type of PDA. For elderly patients with the early-onset type (with an onset before the age of 60 years) and a prolonged illness duration both CBT and pharmacological strategies may be the preferred modality. Again, our findings have to be considered with caution due to small number of patients and not all our overall analyses comparing the effects of the two treatment conditions together yielded significant results



Chapter 9

Summary and general discussion

9.1 Introduction

Anxiety disorders are the most prevalent mental disorders (Kessler et al., 2005a). Highly efficacious pharmacological and psychological treatments have been developed for panic disorder with or without agoraphobia (PD(A)), social phobia, obsessive-compulsive disorder, posttraumatic stress disorder and generalized anxiety disorder (GAD). The effectiveness of both treatment modes has been substantiated in numerous meta-analytic reviews (Abramowitz, 1997; Bakker et al., 2002; Van Balkom et al., 1997; Bisson & Andrew, 2007; Bradley et al., 2005; Fedoroff & Taylor, 2001, Van der Linden et al., 2000; Mitte, 2005a; Mitte, 2005b; Norton & Price, 2007; Seidler & Wagner, 2006; Stein et al., 2000; Taylor, 1996). The development of international guidelines has, accordingly, been based upon these findings[1]. However, and regrettably, these guidelines are almost exclusively founded on randomized controlled trials (RCTs) in adults aged between 18 and 65 years, with an average age of about 35 years. Studies into the treatment of late-life anxiety are scarce, even though anxiety disorders are the most prevalent mental disorders in the elderly (Beekman et al., 1998; Kessler et al., 2005a). Furthermore, less than 10% of all elderly patients suffering from anxiety disorders is offered adequate treatment with cognitive-behavioural therapy (CBT) or antidepressants (De Beurs et al., 1999). In contrast to our elderly, young and middle-aged people suffering from complaints are treated adequately five times more often (Wang et al., 2005b). On the other hand, although not recommended in the guidelines as first-line agents in the management of late-life anxiety disorders, 25 to 43% of all elderly patients are prescribed benzodiazepines (De Beurs et al., 1999; Schuurmans et al., 2005). Frequent use of prescription benzodiazepines is, however, associated with serious drug-related hazards such as an increased risk of falls and fractures, and a possible aggravation of cognitive difficulties (Paterniti et al., 2002; Wang et al., 2001a; Wang et al , 2001b). Furthermore, a critical consideration of the adverse events of SSRIs, the recommended first-line agents for late-life anxiety disorders, showed that the risk of falls and fractures were comparable to those found for both benzodiazepines and antidepressants (Ensrud et al., 2002; Ensrud et al., 2003; Hartikainen et al., 2007; Liu et al., 1998). Given the adverse effects of all major pharmacological agents, CBT should perhaps be more seriously considered as the preferred first-line treatment in late-life anxiety disorders.

But what explains the undertreatment of late-life anxiety disorders? Plausibly, because of their being retired and because they often receive support in and around the home, elderly people may increasingly and successfully avoid anxiety-provoking situations

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(Lindesay, 1991). In addition, proper diagnostic procedures may be complicated by a) a higher prevalence of somatic disorders and overlapping physical symptoms (e.g. pulmonary or cardiovascular diseases; Seung Kim et al , 2001), b) comorbid depression (Beekman et al., 2000), c) the elderly being less open in sharing their psychological problems (Weijnen et al., 2006), d) their attributing psychological symptoms to somatic diseases (Sheehan et al., 2002), and e) a different phenotypical expression (Brenes, 2006; Crittendon & Hopko, 2006; Goldberg et al., 2003, Hunt et al , 2003; Klapow et al , 2002; Lau et al., 2001).

Although it is assumed that age-related differences between younger and older adults suffering from anxiety disorders affect the outcome of targeted treatment (Stanley & Averill, 1999), this has, so far, not been empirically established. In addition, the few findings from RCTs focusing exclusively on elderly patients (60-plus and 65-plus) also tentatively indicate that both CBT and antidepressants are likely optimal options for the management of late-life anxiety disorders (Pinquart & Duberstein, 2007), albeit that the evidence is predominantly limited to GAD or mixed anxiety disorders (Hendriks et al., 2008a; Pinquart & Duberstein, 2007). Inspired by the positive outcomes we obtained with CBT and SSRIs in 60-plus patients suffering from late-life anxiety disorders as reported in two case studies (Hendriks et al., 1999; Hendriks et al., 2008b), and prompted by all the conflicting evidence and the considerable gaps in our knowledge, the work presented in this thesis was aimed at expanding the empirical data on the efficacy of CBT and antidepressants in older adults, in our case patients over 60 years of age diagnosed with anxiety disorders in general, as well as gathering the first empirical evidence for these treatments in elderly patients with confirmed PD(A). Although RCTs and meta-analyses have amply confirmed the effectiveness of both treatments in younger adults, RCTs directly comparing the two approaches in elderly patients suffering from anxiety in general are scarce, while trials evaluating late-life PD(A) are absent, leaving the question whether CBT is to be preferred over specific pharmacological or other psychological treatments unanswered. In the case of PD(A), it has never been tested whether the guideline-recommended treatments with antidepressants or CBT are effective or even feasible in elderly populations. Accordingly, the main research questions posed were:

1. Are CBT and antidepressants similarly effective in the treatment of late-life anxiety disorders?
2. Is CBT more effective than an active control comparison in the management of late-life anxiety disorders?
3. Are both paroxetine and CBT effective and well-tolerated treatments for PD(A) in older adults?
4. Does the content of agoraphobic cognitions differ between younger and older adults suffering from PDA?
5. Is CBT as effective and as well-tolerated in older adults diagnosed with PDA as it has been found to be in younger adults?

6. Are age, age at onset and duration of illness related to outcome in CBT for PDA?
7 Are age and duration of illness related to paroxetine and CBT outcome in late-life PDA?

9.2 Review of the literature and meta-analysis

In Chapters 2 and 3 a systematic overview was given of outcome studies evaluating both psychological and pharmacological treatments for older adults (> 55 years) with anxiety disorders. Although still modest in volume, since the end of the 1990s systematic research into the treatment of late-life anxiety has intensified. To guarantee the methodological quality of the studies, only RCTs in which use was made of valid instruments specifically designed to diagnose anxiety disorders and monitoring outcome were considered. Both reviews served to summarize the evidence on the effectiveness of CBT and pharmacotherapy for late-life anxiety disorders and to establish the efficacy of CBT over other non-pharmacological treatments. Of the 56 potential studies only eight CBTs and three pharmacotherapy trials met the inclusion criteria. All eight studies focused on patients with GAD, or on mixed groups of patients with GAD, PD(A) or social phobia

In Chapter 2 the effect sizes for both the anxiety and depression outcomes were calculated using Cohen's *d*. With large effect sizes (> 0.8) in nine of the ten studies testing CBT and pharmacotherapy relative to a waiting list or treatment as usual, we found convincing evidence of superior treatment effects for CBT and medical interventions for late-life anxiety disorders. The effect sizes for CBT were generally also larger than those for supportive psychotherapy or discussion groups, especially at follow-up. Interestingly, for anxiety CBT efficacy at follow-up had even improved in seven of the eight CBT studies. Moreover, CBT showed a superior effect on accompanying depressive symptoms. It is, moreover, important to bear in mind that, whereas pharmacotherapy was continued during follow-up in all studies, CBT was not.

The results of the meta-analysis presented in Chapter 3 subsequently provided evidence for the effectiveness of CBT in the treatment of anxiety disorders (as based on DSM-IV criteria) occurring later in life Its efficacy was demonstrated in various samples of patients over 60 years of age and not only relative to a waiting-list condition but also relative to an active control condition.

In sum, the empirical data reported thus far showed CBT and antidepressants to be most effective in the treatment of late-life anxiety disorders. The only study that directly compared antidepressant treatment and CBT found a superior effect for the antidepressant. This result should, however, be interpreted with caution, since the effect size of CBT in this study was considerably smaller than those reported in the other studies we reviewed

Our systematic reviews confirmed the lack of RCTs testing the effects of treatment approaches targeting specific late-life anxiety disorders, with the exception of GAD (Mitte, 2005b; Pinquart & Duberstein, 2007) Given that in these latter studies the outcomes obtained in the younger and older adults were comparably favourable, we deemed it relevant to establish whether the other anxiety disorders could also be successfully treated in later life. As the life-time prevalence of PD(A) in this age group is relatively high (2%; Kessler et al, 2005a)), we chose to focus our research reported in this thesis on this specific disorder. Moreover, because in younger adults the agoraphobic type is the most serious and sufferers of this type are most frequently referred to specialized clinics, we were particularly interested in the treatment effects in older patients diagnosed with agoraphobic PD.

9.3 The treatment of late-life panic disorder with and without agoraphobia

The study in Chapter 4 examined the effectiveness of paroxetine and CBT in 49 patients aged on average 70 years (*SD* = 5) all diagnosed with PD(A) who were randomly assigned to 40 mg paroxetine (n = 17), individual CBT (n = 20), or a 14-week waiting list (n = 12). Outcomes, with avoidance behaviour and agoraphobic cognitions being the primary measures, were assessed at baseline, and in weeks 8, 14 (end CBT/waiting list), and 26 (treated patients only), and analyzed using mixed models. All outcome measures showed that both the patients having received CBT and those treated with paroxetine had improved significantly more than the patients in the waiting-list condition, with effect sizes being moderate to large (Cohen's d ranged from 0.6 to 0.9) No differences were found between CBT and paroxetine With one patient (1/20, 5%) dropping out in the CBT and three (3/14, 17.6%) in the paroxetine and one (1/12, 8%) in the waiting-list condition, attrition rates were low. We accordingly concluded that elderly patients with PD(A) responded well to both types of treatment.

One of the study's strong points was that both treatments were well tolerated. With a total attrition rate of 10% (5/49), the loss of patients during this trial was remarkably low compared to other RCTs in elderly people with anxiety disorders, with dropout rates varying between 25 and 30% (Hendriks et al, 2008a; Pinquart & Duberstein, 2007). Our favourable results may be due to the fact that both treatments were delivered at our specialized outpatient clinic, which has a long tradition in the protocolized management of anxiety disorders.

A major concern, on the other hand, is that between 1999 and 2006 we were only able to recruit 49 PD(A) patients over the age of 60 years. This was far less than we had expected based on the prevalence rates reported in epidemiological studies. Other outcome studies

of late-life anxiety disorders also appeared to have had difficulty recruiting participants (e.g. Schuurmans et al, 2006). Besides the explanatory and prohibitive factors mentioned earlier in the introduction of this chapter, and although speculative, two other aspects may have played a role here. Both mental health professionals and patients, as well their relatives, may have low expectations regarding the outcome of interventions at this late stage in life, with the prolonged course of the disorder having caused the loss of confidence in recovery (Klap et al , 2003). Alternatively or additionally, referral to a mental health facility may trigger a fear of stigmatization (Sirey, Bruce, Alexopoulos, Perlick, Raue, Friedman et al., 2001).

Finally, we were somewhat surprised by the relatively low total baseline scores for agoraphobic cognitions we obtained in our sample, even though an earlier study also recorded lower scores for their older PD(A) patients than for their younger patients (Sheikh et al, 2004). This raised two questions: do older people with PD(A) have different agoraphobic cognitions than their younger counterparts, or do these cognitions decline with increasing age? To try and resolve these issues, we conducted the study reported in Chapter 5.

9.4 Agoraphobic cognitions in younger and older patients with panic disorder with agoraphobia

In Chapter 5 we reported on our comparative study of the frequency and intensity of agoraphobic cognitions in 48 older (≥ 60 years, range 60 to 85 years) and 157 younger adults (< 60 years) with PDA. The 60-plus patients had a significantly lower mean Agoraphobic Cognitions Questionnaire (ACQ) total score than their younger counterparts: their scores on the items *fear of going crazy*, *acting foolishly*, *losing control*, *passing out*, and *having a brain tumour* were significantly lower. This differential effect at the ACQ-item level suggests that some cognitions appear less relevant for agoraphobic PD in later life. Future research should establish whether and which age-related cognitions are missing in the currently widely used self-report instruments. In our study we did not verify whether late-life PDA is characterized by different agoraphobic cognitions than it is in younger and middle-aged patients. Although preliminary, we concluded that the ACQ is not the most suitable self-report tool to assess patients with late-life PDA. However, to date there is no alternative inventory for agoraphobic cognitions. As the total mean scores for the frequency and intensity of avoidance behaviour did not differ between the two age-groups, we made the recommendation to base the severity of late-life PDA on the severity of agoraphobic avoidance.

In clinical practice many therapists consider manual-based CBT inappropriate, being convinced that patients need personalized treatment plans adapted to their individual

needs, with which stance they prevent CBT from being offered to specific target groups like elderly PD patients. Empirical evidence for these assumptions is, however, hardly available (Wilson, 1996). In addition, some authors recommend age-specific modifications in the CBT manual and delivery in a group format (Stanley & Averill, 1999). Yet, the evidence to substantiate these assumptions is again scarce. Until now, only Mohlman and colleagues (2003) have compared both standard and age-specific CBT to a waiting-list control condition. Although the modified CBT showed better results than the standard programme, the study was limited by its small sample size (n = 42) and the lack of a direct comparison of the standard and modified interventions.

As no studies were available that directly compared the outcomes of protocolized CBT in younger and older adults with PD(A) without age-specific modifications, we decided to do so ourselves and the results of this comparison are described in the following section.

9.5 Cognitive-behavioural therapy for panic disorder with agoraphobia in older people: A comparison with younger patients

Chapter 6 describes the results of our comparison of the outcomes obtained with the same, protocol-based CBT programme in 141 younger and middle-aged patients diagnosed with PDA (average age 35 years; SD = 10) and 31 older patients (average age 68 years; SD = 5). The older patients improved significantly more with respect to agoraphobic avoidance than their younger counterparts. No between-group differences were found for post-treatment agoraphobic cognitions and the secondary outcomes, general level of psychopathology and depressive symptoms. Although not significant (p = .06), with 2/31 (6%) and 31/141 (22%) attrition rates were numerically lower for the 60-plus group than they were for the younger adults. The results thus showed the standard, protocolized CBT for PDA to be feasible for patients over the age of 60 years, yielding even better outcomes than obtained in younger adults. The need to adapt the existing CBT protocols for PDA to elderly patients hence does not appear to be urgent or warranted although it cannot altogether be ruled out that modifications may produce even better outcomes.

PD(A) onset usually occurs at a relatively young age: in 75% of all patients the complaints manifest themselves before their 40th year, while only 1% have an onset at age 63 or later (Kessler et al., 2005a). As PD(A) is relatively prevalent in older people, the symptoms have run a chronic course in most elderly patients. However, epidemiological surveys show there is a small population that first develops symptoms after the age of 60. Proportionally, with rates ranging from 3 to 6%, this group is relatively frequently represented in clinical populations (Raj, Corvea & Dagon, 1993; Segui et al, 2000, Sheikh et al, 1991). It is widely

assumed that the effectiveness of CBT for anxiety disorders decreases with age, but the empirical grounds for this presumption are, however, weak. Therefore, in Chapters 7 and 8 we put these assumptions to the test.

9.6 The relationship between age-related variables and treatment outcome in late-life PDA

In Chapter 7 we examined the effects of age, age at onset, and duration of illness (DOI) on CBT outcomes in 172 PDA patients stratified at age 60 years. As expected, the severity of both agoraphobic avoidance and agoraphobic cognitions were the most important predictors of outcome in the overall sample. Age was not related to outcome, with the exception of a superior reduction of agoraphobic avoidance in the elderly subgroup. In this latter subgroup, a higher age, a later onset, and a short DOI resulted in less agoraphobic avoidance at outcome. We felt the results merited the conclusion that in PDA old(er) age does not reduce the effectiveness of protocolized CBT.

The differential predictive values of age and DOI on the outcomes of paroxetine and cognitive-behavioural therapy (CBT) in late-life PDA were evaluated in Chapter 8.

Forty-nine patients aged 60+ years with a confirmed diagnosis of PDA were randomly assigned to 40 mg/d paroxetine (n = 17), individual CBT (n = 20), or a waiting-list control condition (n = 12). The main finding was that age had no impact on treatment modality outcome. Furthermore, a higher age at onset and a shorter illness duration were predictors of superior outcomes following CBT, while the variables did not influence the treatment effects of paroxetine. These findings suggest that CBT may be the treatment of choice for the late-onset type of PDA. For elderly patients with the early-onset type, i.e. an onset before the age of 60 years, and a prolonged illness duration, both CBT and pharmacological strategies may be the preferred modalities. Our findings have to be considered with caution, however, due to small number of patients and because not all our overall analyses comparing the effects of the two treatment modalities together yielded significant results.

9.7 Methodological considerations

Our review of the literature on pharmacological and psychological treatments of late-life anxiety disorders (Chapter 2) was restricted due to the quality criteria we set. We limited our search to controlled studies and this yielded only a small number whose methodological quality merited evaluation. In addition, the sample sizes used in the studies we reviewed were relatively small and attrition rates often exceeded 20%, which is the percentage the

Cochrane Study Group uses as the upper limit for attrition. Moreover, most studies only included patients with GAD, and, with ages between 61 and 72 years, the patients treated were still relatively young The small number (n = 3) of pharmacological RCTs prevented a quantitative analysis, which is why we, in our meta-analytic review (Chapter 3) only discussed the results on the psychological interventions for late-life anxiety disorders. Yet again, the meta-analysis suffered the same limitations as our literature review and its results can thus only be generalized to 'relatively younger' older patients with GAD.

Our RCT of paroxetine and CBT for the treatment of late-life PD(A) using a waiting-list control condition (Chapter 4) was the first to directly compare two guideline-recommended treatments. However, its statistical power was limited by its relatively small sample size (n = 49) Our conclusions should therefore be interpreted with caution We also omitted to use a placebo condition for both treatment modalities. However, both treatments yielded effect sizes comparable to those reported in meta-analytic reviews for young and middle-aged adults with PD(A) (Mitte, 2005), which argues against a discernible placebo effect in our study Furthermore, the self-report instruments we used to evaluate treatment effects in our 60-plus cohort have, so far, only been validated in younger PD(A) populations (18-65 yrs), which may imply that the scales are less valid for patients over the age of 65 years. Yet, and although few in number, this is countered by the available validation studies in 60-plus samples that found no objections for their use in this age range (Fuentes et al., 2000; Crittendon et al , 2006). Finally, as our findings were limited to relatively young (average age: 70 years) and relatively healthy elderly patients, the results cannot be generalized to their older and frailer peers

The aforementioned reservations against the use of self-report questionnaires and the problems associated with the specificity of the demographic characteristics of our study population also apply to the subsequent studies we conducted.

The main limitation of the study we conducted into the potential differences in the content of agoraphobic cognitions in older and younger adults with PDA (Chapter 5) was that we failed to perform a quantitative analysis on agoraphobic cognitions that were not included in the Agoraphobic Cognitions Questionnaire (ACQ).

The relatively small size of the 60-plus group (n = 31) in our comparison of PDA-specific CBT for younger and older adults (Chapter 6) reduced its statistical power, which is why our conclusions warrant cautious interpretation. Furthermore, we cannot rule out a selection bias in the 60-plus group. In contrast to younger adults, elderly people with PDA are far more often underdiagnosed and undertreated (De Beurs et al., 1999; Kessler et al., 2005b), which may imply that, perhaps, the ability of the elderly patients in our study to express their complaints adequately and make clear that they wished to be referred for specialized treatment was above average.

The study reported in Chapter 7 examined the relationship between age, age at onset, and duration of illness (DOI) and the outcome of PDA treatment. However, defining early and late age of onset in PD(A) is rather complex. In epidemiological and clinical studies, a PD(A) onset between the ages of 30 and 50 years is defined as late age of onset (Katerndahl & Talamantes, 2000; Sheikh et al , 2004). Yet, such a definition largely ignores the influence of the ageing process on the symptoms and severity of the PD(A). Therefore, in line with the generally accepted cut-off age between 55 and 65 years, and similar to what other researchers (Alexopoulos et al., 1993, Reynolds et al., 1998; Segui et al, 2000) did before us, we chose 60 years as the lower limit for the definition of late age of onset. Furthermore, as age of onset and hence DOI are, by definition, based on retrospectively collected data, their reliability is, of course, limited. Finally, in Chapter 8 we showed that CBT and paroxetine yielded differential outcomes in late-life PD(A) and hence tentatively concluded that CBT was the preferred modality for older patients with a late age of onset and shorter DOI and paroxetine the treatment of choice for older patients with an early age of onset and long-standing DOI Nevertheless, it should be borne in mind that sample sizes were small and that the findings were not consistently statistically significant when both treatments were compared and analyzed in one model.

This critical reflection on the research reported in this thesis is not complete without returning to a vital issue in this type of investigation. Worldwide, the recruitment and (extended) participation of elderly people in RCTs evaluating outcomes of treatments for late-life anxiety remains particularly difficult. Although prior to our studies the management of GAD in later life had been frequently evaluated, for the other anxiety disorders, most notably panic disorder, empirical findings were still scarce or even absent, the underlying factors for which have been discussed above. It is therefore unique that the effectiveness of both CBT and SSRI treatment in the management of late-life PD(A) have now been investigated in a randomized and controlled design for the first time and that the outcome of non-adapted manualized CBT for PDA has been directly compared in older (> 60 years) and younger (18-59 years) patients.

9.8 Conclusions and clinical implications

At the highest level of empirical evidence, i.e. the meta-analytical level, the results of our studies only provide sufficient proof for the efficacy of CBT in the psychological treatment of late-life anxiety disorders, prompting the inference that in later life CBT is to be preferred over other psychological interventions Moreover, although recommendations have been made to adapt protocolized CBT for anxiety disorders to the specific needs

of the elderly to enhance outcome (Schuurmans, 2005), the empirical grounds for such age-specific modifications are weak. To date, only one pilot study (n = 42; Mohlman et al., 2004) comparing age-adapted and standard CBT showed better results for the adapted protocol The other available and methodologically sounder studies using larger samples showed no differences between two such treatment versions (Stanley et al, 2003a, Wetherell et al , 2003). Furthermore, comparing the effect sizes obtained with CBT in elderly adults with anxiety disorders to those reported for younger and middle-aged patients, only one study found a lower effect size for CBT in the elderly group (Schuurmans et al., 2006), while the other studies reported results for their older patients that were similar to those obtained in relatively younger adults (this thesis Chapter 2 and Pinquart & Duberstein, 2007). In short, it is too precipitate to argue for age-specific adaptations to be introduced in the available and evidence-based CBT protocols for the treatment of anxiety disorders. Also the suggestion that antidepressants should be preferred in the treatment of late-life anxiety disorders (Pinquart & Duberstein, 2007) is preliminary considering the fact that empirical data of direct comparisons of CBT and antidepressants are lacking. Moreover, the relative risks of fractures and slip-and-fall accidents in elderly patients treated with antidepressants or benzodiazepines are similarly high (see e.g. Hartikainen et al., 2007).

Our PD(A) studies showed both CBT and paroxetine to be effective in elderly patients, with slightly better outcomes for CBT in patients with PDA onset at an older age. Both treatments were well tolerated and attrition was low Although unsubstantiated, we attribute the low attrition rates to the fact that the treatment was provided in our dedicated outpatient clinic where therapists are specialized in protocolized CBT for anxiety disorders, which may not always have been the case in the other studies. Additionally, in such specialized settings like ours, systematic attention is paid to adherence-enhancing interventions, which may also have contributed to the low dropout

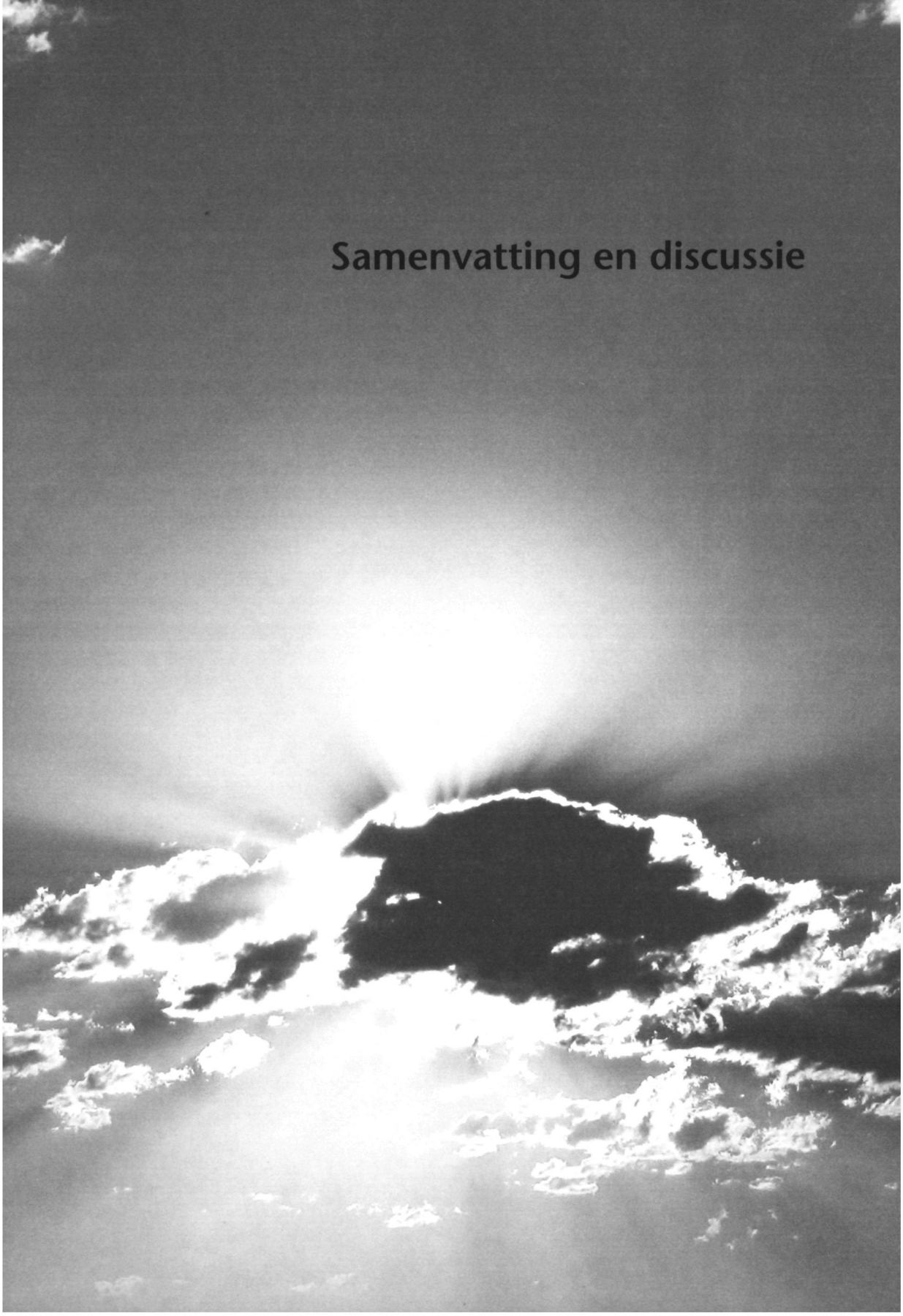
Finally, and perhaps most saliently, age was never significantly negatively associated with outcome in our studies evaluating treatments of late-life PDA delivered according to the existing guidelines, and neither were age of onset and duration of illness.

9.9 Recommendations for clinical practice and future research

It is important to mention again that our samples, as in other trials of late-life anxiety disorders, were relatively small. This, obviously, warrants replication of our findings in larger cohorts. Additionally, as the prevalence of these disorders is high (Kessler et al., 2005) and quality of life is impaired similarly to that in depression (Wetherell et al., 2004), more research into the treatment of late-life anxiety disorders is truly indispensable We, therefore, propose the following recommendations:

1. Education of patients and general practitioners (GPs) needs to be stepped up. Despite various efforts to boost the recruitment of elderly patients with PD(A) for our studies, among which coverage of the topic and our research in local newspapers, the referral rate remained low, drawing out our study accordingly. Arguably, the lack of knowledge about the symptoms and available treatments in primary care settings that prevent an adequate and timely identification and targeted treatment of late-life anxiety disorders remains a major concern. Providing elderly people as well as referrers (mostly GPs) with (more) targeted information about anxiety disorders in later life may contribute to a better recognition and treatment of these prevalent disorders.
2. Offering dedicated consulting hours or setting up counselling clinics in local health centres or GP (group) practices should be considered. Many older people are rather averse to being referred to a mental health facility, which is probably caused by a fear of stigmatization. Especially in elderly patients with anxiety disorders offering targeted screening and treatment by specialized mental health professionals at the familiar local health centre or GP's office may reduce such reservations.
3. RCTs should be conducted in accordance with the existing guidelines for the treatment of specific anxiety disorders to answer the following three main questions:
   a Can elderly people with specific anxiety disorders be treated as effectively as younger and middle-aged adults when applying the existing guidelines?
   b If not, which variables negatively affect outcome (most)?
   c Can these variables be neutralized by adapting the existing treatment protocols to the target group?
4. Prospective studies need to examine the effects of ageing on the phenomenology of late-life anxiety disorders to help improve diagnostic and screening procedures.

Prompted by the findings reported in this thesis and to help convey the current knowledge of the management of anxiety disorders in elderly patients with as much transparency as possible, we have prepared two protocols on the psychological and pharmacological treatments of late-life anxiety disorders for the Cochrane Database of Systematic Reviews. In these protocols we provide a summary of the available evidence and present the evidence gathered in this thesis, to which we aim to periodically add new empirical data on the topic (see Appendices A and B).



Samenvatting en discussie

Angststoornissen zijn de meest voorkomende psychiatrische stoornissen (Kessler et al., 2005a). Voor specifieke angststoornissen zoals paniekstoornis met/zonder agorafobie, sociale fobie, obsessief-compulsieve stoornis, posttraumatische stressstoornis en gegeneraliseerde angststoornis zijn effectieve farmacologische en psychologische behandelingen ontwikkeld. Hiervan is de werkzaamheid definitief vastgesteld in een groot aantal gepubliceerde meta-analyses (Abramowitz, 1997; Bakker et al., 2002; Van Balkom et al., 1997; Bisson & Andrew, 2007, Bradley et al., 2005; Fedoroff & Taylor, 2001; Van der Linden et al , 2000; Mitte, 2005a; Mitte, 2005b; Norton & Price, 2007; Seidler & Wagner, 2006; Stein et al., 2000; Taylor, 1996) Op basis daarvan zijn zowel nationale als internationale richtlijnen voor behandeling opgesteld[1]. Een belangrijke omissie is dat deze behandelrichtlijnen gebaseerd zijn op wetenschappelijk onderzoek bij volwassen van 18 tot 65 jaar met een gemiddelde leeftijd van ongeveer 35 jaar. Hoewel angststoornissen ook bij ouderen tot de meest voorkomende psychiatrische stoornissen behoren (Beekman et al , 1998; Kessler et al., 2005a), is onderzoek naar de behandeling hiervan in deze leeftijdsgroep uiterst beperkt. Bovendien blijkt uit bevolkingsonderzoek, dat minder dan 10% van de ouderen met een angststoornis hiervoor een adequate behandeling krijgt (De Beurs et al., 1999) in tegenstelling tot 50% bij jongere volwassenen (Wang et al., 2005b). Opvallend is dat ouderen met angststoornissen relatief vaak benzodiazepinen gebruiken (25-43%) (De Beurs et al., 1999; Schuurmans et al., 2005), terwijl deze juist op oudere leeftijd gepaard gaan met belangrijke bijwerkingen (verhoogd risico op (onge)vallen, amnesie en afhankelijkheid) en voor geen enkele angststoornis eerste keus zijn. Wanneer kritisch naar de eerste keus stappen gekeken wordt (SSRI of cognitieve gedragstherapie (CGT)), zou gezien de bijwerkingen van SSR's (vergelijkbaar valrisico als benzodiazepinen (Ensrud et al., 2002; Ensrud et al., 2003; Hartikainen et al., 2007; Liu et al., 1998)), voor ouderen misschien wel een voorkeur voor CGT moeten worden uitgesproken.

Verschillende factoren liggen ten grondslag aan de onderbehandeling van angststoornissen bij ouderen. Ten eerste is vermijdingsgedrag moeilijk op te sporen bij ouderen omdat het sociaal-maatschappelijk appel minder is, er dus minder externe druk is om op zoek te gaan naar een gerichte behandeling en er meer ondersteuning vanuit de sociale omgeving wordt aangeboden (Lindesay, 1991). Ten tweede is bij ouderen de diagnostiek complexer door a) een hogere prevalentie van somatische aandoeningen die symptomen geven die overlappen met somatische angstequivalenten (o.a. Seung Kim et al., 2001), b) overlap met depressieve stoornissen (hoewel die bij slechts 25% van de angststoornissen op hogere leeftijd speelt (Beekman et al., 2000)), c) terughoudendheid bij de huidige generatie ouderen om psychische problemen bespreekbaar te maken (Weijnen et al.,

1 http //www nice org uk/guidance/index jsp
http //www psych org/MainMenu/PsychiatricPractice/PracticeGuidelines_1 aspx
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2006) of de neiging deze toe te schrijven aan somatische problemen (Sheehan et al., 2002) en tot slot d) een mogelijk andere, soms mildere fenotypische expressie (Brenes, 2006; Crittendon & Hopko, 2006; Goldberg et al., 2003; Hunt et al., 2003; Klapow et al., 2002, Lau et al., 2001). Hoewel verondersteld wordt dat verschillen tussen angststoornissen op jongere en oudere leeftijd het effect van gerichte behandeling beïnvloeden (Stanley & Averill, 1999), is dat nooit empirisch vastgesteld. Daarentegen wijzen gerandomiseerde, gecontroleerde behandelstudies juist op vergelijkbare effecten van psychologische en farmacologische behandeling bij (jong)volwassenen en ouderen met angststoornissen (Pinquart & Duberstein, 2007).

Een belangrijke beperking bij het onderzoek onder ouderen is dat tot nu toe de focus vooral lag op de behandeling van gegeneraliseerde angststoornis of angststoornissen in algemene zin (Pinquart & Duberstein, 2007). Behandelstudies naar specifieke angststoornissen bij ouderen, zoals paniekstoornis met/zonder agorafobie, zijn niet voorhanden. Geïnspireerd door succesvolle praktijkervaringen met het behandelen van angststoornissen op oudere leeftijd en vanwege de schaarse empirische gegevens bij de oudere leeftijdscategorie is het doel van dit proefschrift een bijdrage te leveren aan het vergaren van meer empirische gegevens over de effectiviteit van cognitieve gedragstherapie bij angststoornissen op oudere leeftijd in algemene zin, en de farmacologische en cognitief-gedragstherapeutische behandeling van paniekstoornis met/zonder agorafobie op oudere leeftijd in het bijzonder. Gezien de vooroordelen ten aanzien van de behandelmogelijkheden bij ouderen, werd specifiek onderzoek gedaan naar het effect van leeftijd, de ontstaansleeftijd van de paniekstoornis en de ziekteduur op het behandelresultaat. De onderzoeksvragen luidden als volgt

1. Zijn zowel CGT als antidepressiva vergelijkbaar effectief in de behandeling van ouderen met angststoornissen?
2. Is CGT effectiever dan andere niet-farmacologische interventies bij de behandeling van ouderen met angststoornissen?
3. Zijn zowel paroxetine als CGT effectief bij de behandeling van ouderen met een paniekstoornis met/zonder agorafobie en worden beide behandelingen goed verdragen?
4. Is de inhoud van de agorafobische cognities bij (jong)volwassenen en ouderen met een paniekstoornis met agorafobie verschillend?
5. Is CGT voor paniekstoornis met agorafobie bij ouderen even effectief en wordt deze behandeling net zo goed verdragen als bij (jong)volwassenen?
6. Zijn leeftijd, ontstaansleeftijd en ziekteduur geassocieerd met het behandelresultaat van CGT voor paniekstoornis met agorafobie?
7. Zijn bij ouderen met een paniekstoornis met agorafobie leeftijd en ziekteduur geassocieerd met het behandelresultaat van paroxetine en/of CGT?

Literatuuroverzicht en meta-analyse

In hoofdstuk 2 en 3 wordt een systematische literatuurstudie gepresenteerd van de tot nu toe verschenen behandelstudies bij ouderen (> 55 jaar) met angststoornissen. Sinds het einde van de jaren '90 van de vorige eeuw wordt er, hoewel bescheiden in volume, systematisch onderzoek verricht naar de behandeling van angststoornissen op oudere leeftijd. Om te voorkomen dat de geïncludeerde studies van onvoldoende methodologische kwaliteit zouden zijn en onvoldoende vergelijkbaar, werden alleen gerandomiseerde, gecontroleerde studies opgenomen waarin gebruikt werd gemaakt van valide instrumenten voor diagnostiek en monitoring van het behandelresultaat. Het doel was na te gaan of angststoornissen ook bij ouderen effectief te behandelen zijn met zowel farmacotherapie als CGT en of er bewijs was dat CGT effectiever was dan andere psychologische interventies. Van de 56 potentiële studies naar behandeling van angststoornissen bij ouderen, voldeden slechts acht CGT- en drie farmacotherapiestudies aan de inclusiecriteria. Alle studies hadden betrekking op patiënten met een gegeneraliseerde angststoornis of een gemengde groep patiënten met een gegeneraliseerde angststoornis, paniekstoornis of sociale fobie.

In hoofdstuk 2 werden de effect sizes volgens Cohens *d* berekend voor de gemeenschappelijke angst- en depressieschalen. De effect sizes met betrekking tot de voor- en nameting/follow-up binnen behandelgroepen met farmacotherapie en CGT waren groot (> 0.8) in zeven van de acht CGT-studies en in alle farmacotherapiestudies. In vergelijking met de controlecondities, werden matig tot grote effect sizes gevonden (Cohens d = 0.3 tot 0.8), waarbij farmacotherapie superieur bleek aan CGT (1 studie).

In hoofdstuk 3 werd een meta-analyse uitgevoerd naar het effect van CGT. Behandeling met CGT bleek zowel superieur aan een wachtlijstcontroleconditie als aan een actieve controleconditie waarin patiënten (niet-specifieke) aandacht of ondersteunende psychologische interventies kregen aangeboden.

De conclusie van beide overzichten is dat zowel CGT als antidepressiva effectief zijn voor de behandeling van angststoornissen op oudere leeftijd en dat CGT effectiever is dan andere niet-farmacologische interventies. De enige studie waarin farmacotherapie en CGT direct vergeleken werden liet een superieur effect voor farmacotherapie zien. Dit resultaat moet echter met enige voorzichtigheid geïnterpreteerd worden, aangezien het effect van CGT in deze studie duidelijk kleiner was dan het effect van CGT in de andere CGT-studies.

Deze systematische literatuurstudies bevestigden de afwezigheid van gecontroleerde behandelstudies naar angststoornissen bij ouderen anders dan de gegeneraliseerde angststoornis. Aangezien bij de behandeling van de gegeneraliseerde angststoornis vergelijkbare effecten werden gevonden als in jongere populaties (Mitte, 2005b; Pinquart & Duberstein, 2007), is het belangrijk na te gaan of de andere angststoornissen op oudere leeftijd evenzeer succesvol behandeld kunnen worden. In dit proefschrift werd

ervoor gekozen de behandelmogelijkheden van ouderen met een paniekstoornis nader te onderzoeken omdat de prevalentie daarvan gedurende het leven bij deze leeftijdsgroep relatief hoog is, namelijk 2% (Kessler et al , 2005a). Aangezien bij jongere volwassenen met een paniekstoornis met/zonder agorafobie de agorafobische variant als de meest ernstige variant wordt beschouwd en deze relatief frequent voor behandeling naar gespecialiseerde poliklinieken worden doorverwezen waren wij vooral geïnteresseerd in oudere patiënten met deze variant

Behandeling van ouderen met een paniekstoornis met/zonder agorafobie

De studie in hoofdstuk 4 was gericht op het vaststellen van de effectiviteit van CGT en paroxetine voor ouderen met een paniekstoornis In totaal werden 49 patiënten geïncludeerd met een gemiddelde leeftijd van 70 (*SD* = 5) jaar. Hiervan werden 20 patiënten toegewezen aan de behandelconditie met CGT (14 sessies, protocollair), 17 aan de medicatieconditie (paroxetine 40 mg per dag) en 12 patiënten aan de wachtlijst-conditie. De uitval was 5% (1/20) in de CGT-conditie, 18% (3/17) in de paroxetineconditie en 8% (1/12) in de wachtlijstconditie. Beide behandelingen waren significant beter dan de controleconditie op primaire uitkomstmaten (agorafobisch vermijdingsgedrag en agorafobische cognities) en de secundaire uitkomstmaat algemene psychopathologie met middelmatige tot grote effectgroottes (Cohens *d* varieerde van 0.6 tot 0.9). Er was geen verschil tussen behandeling met CGT of paroxetine.

Een belangrijk aandachtspunt is dat zowel de farmacologische als de psychologische behandeling goed werd verdragen. Met een totale uitval van 5 van de 49 patiënten (10%) is deze opvallend gering in vergelijking met andere behandelstudies bij ouderen met angststoornissen (meestal tussen de 25 en 30% (Hendriks et al., 2008a; Pinquart & Duberstein, 2007). Een mogelijke verklaring is het feit dat beide behandelingen werden uitgevoerd op een gespecialiseerde polikliniek met een lange traditie in de uitvoering van geprotocolleerde behandeling van angststoornissen.

Een tweede belangrijk aandachtspunt is dat tussen 1999 en 2006 slechts 49 patiënten van 60 jaar of ouder met een paniekstoornis met/zonder agorafobie werden geïncludeerd. Dit is fors minder dan verwacht mag worden op basis van prevalentiecijfers in bevolkingsstudies en in het verzorgingsgebied van onze polikliniek. Eerdere studies naar oudere patiënten met angststoornissen blijken eveneens moeite te hebben gehad met de recrutering (o.a. Schuurmans et al., 2006). Hoewel men enkel kan speculeren naar een verklaring hiervoor, zijn de volgende aspecten, naast de eerdergenoemde factoren (zie de inleiding van deze samenvatting), mogelijk van belang. Zowel hulpverleners, patiënten zelf als hun omgeving kunnen lage verwachtingen hebben van de behandelmogelijkheden op oudere leeftijd voor vaak al lang bestaande klachten waardoor het vertrouwen in herstel gering zal zijn (Klap et al., 2003). Daarnaast zou er sprake kunnen zijn van angst voor stigmatisering bij doorverwijzing naar een instelling voor geestelijke gezondheidzorg (Sirey et al., 2001).

Een opvallende bevinding ten slotte was de relatief lage totaalscore op de vragenlijst voor agorafobische cognities. Een eerdere studie vond eveneens lagere scores voor agorafobische cognities bij oudere patienten met een paniekstoornis in vergelijking met jongere patienten (Sheikh et al., 2004). Dit roept de vraag op of ouderen met een paniekstoornis andere angstcognities hebben of dat specifieke cognities afnemen met het ouder worden en dit een aanwijzing zou kunnen zijn voor een leeftijdsgerelateerde afname in ernst van de paniekstoornis. Om dit te onderzoeken werd de volgende studie verricht.

Agorafobische cognities bij ouderen en (jong)volwassenen met een paniekstoornis met agorafobie

In hoofdstuk 5 werden de agorafobische cognities van 48 oudere (≥ 60 jaar, range 60 – 85 jaar) patienten met een paniekstoornis met agorafobie vergeleken met die van 157 jongere patienten (< 60 jaar) De oudere patienten hadden een significant lagere totaalscore op de Agoraphobic Cognitions Questionnaire (ACQ). Ouderen hadden op elke item gemiddeld een lagere score, waarbij significant lagere scores gevonden werden voor de angstgedachte om gek te worden, om zich belachelijk te gedragen, om de controle te verliezen, om flauw te vallen en de angstgedachte een hersentumor te hebben. Geconcludeerd werd dat het differentiele effect op itemniveau aangeeft dat bepaalde agorafobische cognities bij paniekstoornis met agorafobie op oudere leeftijd mogelijk minder relevant zijn dan bij jongere volwassenen met een paniekstoornis. Een beperking van de studie is dat niet is nagegaan of ouderen met paniekstoornis met agorafobie wellicht andere agorafobische cognities hebben. Deze bevindingen zetten dus twijfels bij het gebruik van de ACQ bij ouderen. Vooralsnog is er echter geen geschikt onderzoeksinstrument voor het beoordelen van de agorafobische cognities bij ouderen met een paniekstoornis met agorafobie. Omdat er geen verschil was in agorafobische vermijding tussen beide leeftijdsgroepen is het advies om bij het beoordelen van de ernst van de paniekstoornis met agorafobie bij ouderen vooral af te gaan op ernst van de agorafobische vermijding.

In de literatuur over psychotherapie bij ouderen wordt vaak gesproken over leeftijdspecifieke aanpassingen in de behandeling. In het kader van de behandeling van angststoornissen bij ouderen, is slechts 1 studie bekend waarbinnen een gerandomiseerde studieopzet een standaard- versus een aangepaste vorm van CGT bij ouderen werd toegepast (Mohlman et al., 2003). Hoewel de aangepaste vorm betere resultaten liet zien, kunnen hier gezien de beperkte omvang van de studie (n = 42) geen harde conclusies aan verbonden worden. Tevens zijn eerdere behandelstudies naar angststoornissen bij ouderen vaak in groepsvorm uitgevoerd vanuit het idee dat dit juist voor ouderen prettig is (Stanley et al., 1996). Bevindingen bij jongere patiënten met angststoornissen wijzen echter uit dat de effecten van groepsbehandeling geringer zijn in vergelijking met individuele behandeling.

Omdat een vergelijking tussen de behandeling van ouderen en jongeren met een bestaand behandelprotocol zonder aanpassing aan de oudere leeftijdsgroep nooit is uitgevoerd, werd dit door ons nader onderzocht.

CGT voor paniekstoornis met agorafobie: een vergelijking tussen ouderen en (jong) volwassenen

In hoofdstuk 6 werd de effectiviteit van een niet aan de oudere leeftijd aangepaste, geprotocolleerde CGT voor paniekstoornis met agorafobie bij 31 oudere patienten (≥60 jaar, gemiddelde leeftijd 68) vergeleken met 141 jongere patienten. Opvallend was de significant grotere verbetering op agorafobisch vermijdingsgedrag in de oudere leeftijdsgroep in vergelijking met de jongere patienten. Er werden geen significante verschillen in behandeleffect gevonden tussen de twee leeftijdsgroepen op de andere primaire uitkomstmaat (agorafobische cognities) en de secundaire uitkomstmaten (algemeen niveau psychopathologie en depressieve symptomen). De uitval in de jongere leeftijdsgroep (31/141, 22%) was numeriek hoger dan in de oudere leeftijdsgroep (2/31, 6%), maar dit verschil bleek niet significant ($p = 0.06$).

Geconcludeerd werd dat geprotocolleerde CGT even goed verdragen werd door de oudere patienten en dat zij zelfs in vergelijking met de jongere patienten meer profiteerden van het CGT-protocol met betrekking tot afname van de agorafobische vermijding. Het aanpassen van de bestaande CGT-behandelprotocollen aan oudere patienten lijkt vooralsnog niet nodig.

Vanwege onderdiagnostiek en daarmee samenhangende onderbehandeling bestaat de paniekstoornis, die veelal op jongere leeftijd onstaat, bij oudere patienten al vele jaren. Daarnaast blijkt uit bevolkingsonderzoek dat er een kleine groep ouderen is die voor het eerst na het 60e levensjaar een paniekstoornis ontwikkelt (Kessler et al., 2005a). Deze groep blijkt in klinische populaties relatief frequent vertegenwoordigd te zijn met percentages variërend van 3-6% (Segui et al., 2000, Sheikh et al., 1991; Raj, Corvea & Dagon, 1993). Omdat in de praktijk veel behandelaren een hogere leeftijd en/of langere ziekteduur associeren met een slechter behandelresultaat, werd dit in de studies in hoofdstuk 5 gericht onderzocht.

Het verband tussen leeftijdsgerelateerde variabelen en het behandelresultaat

De studie in hoofdstuk 7 betrof dezelfde populatie als in hoofdstuk 6. Onderzocht werd de relatie tussen leeftijd, de ontstaansleeftijd van de stoornis en de ziekteduur met het behandelresultaat. Het bleek dat leeftijd geen invloed had op het behandelresultaat Echter, oudere leeftijd en het ontstaan van de paniekstoornis op een leeftijd van boven de 60 jaar voorspelde een sterkere verbetering van de agorafobische vermijding. Geconcludeerd werd dat het hebben van een oudere leeftijd zeker niet geassocieerd mag

worden met een afgenomen effectiviteit van geprotocolleerde CGT voor paniekstoornis met agorafobie.

De studie in hoofdstuk 7 was gericht op het onderzoeken van leeftijdsgerelateerde variabelen en ziekteduur met betrekking tot de effecten van paroxetine 40 mg per dag (n = 17) of geprotocolleerde CGT (n = 20) bij patienten van 60 jaar of ouder met een paniekstoornis met agorafobie. Gevonden werd dat een hogere leeftijd en een korte ziekteduur een beter behandeleffect voorspelden bij geprotocolleerde CGT, maar niet voor behandeling met paroxetine. De conclusie was dat onafhankelijk van de behandelmodaliteit leeftijd niet van invloed is op de uitkomst voor behandeling van paniekstoornis met agorafobie op oudere leeftijd. Tevens kwam naar voren dat een hoge ontstaansleeftijd in combinatie met een kortere ziekteduur een relatief gunstig effect van de CGT voorspelde, terwijl ontstaansleeftijd en ziekteduur niet van invloed waren op het effect van paroxetine. Hieruit zou voorzichtig afgeleid kunnen worden dat bij een vroege ontstaansleeftijd en dus ook een lang ziektebeloop ouderen met een paniekstoornis mogelijk beter met paroxetine behandeld kunnen worden dan met CGT. Een belangrijke beperking van beide studies is echter de geringe groepsgrootte van de groep oudere patienten. Dit betekent dat het slechts voorlopige bevindingen betreft en dat replicatie in grotere onderzoekspopulaties nodig is om de betekenis van leeftijd, ontstaansleeftijd en duur van de klachten verder te ontrafelen bij oudere patienten.

Methodologische overwegingen

De belangrijkste beperking van het literatuuroverzicht (hoofdstuk 2) is in de eerste plaats het bescheiden aantal gecontroleerde studies van goede methodologische kwaliteit betreffende de farmacologische en psychologische behandeling van angststoornissen bij ouderen. Daarnaast zijn de steekproefgroottes relatief gering en is het uitvalpercentage vaak meer dan 20% wat als belangrijke bovengrens wordt gehanteerd door de Cochrane Study Group. Bovendien hebben de meeste studies alleen patienten met een gegeneraliseerde angststoornis onderzocht en is bij alle studies de gemiddelde leeftijd relatief laag, namelijk 61 tot 72 jaar. Het aantal behandelstudies met farmacologische interventies was zo gering dat een goede kwantitatieve analyse niet mogelijk was. Daarom betreft de meta-analyse (hoofdstuk 3) enkel een kwantitatieve analyse van behandelstudies met psychologische interventies bij ouderen met angststoornissen Ook voor de meta-analyse gelden bovengenoemde beperkingen, waardoor de resultaten enkel generaliseerbaar zijn naar relatief jongere ouderen met een gegeneraliseerde angststoornis.

De studie (hoofdstuk 4) naar de effecten van paroxetine en CGT bij ouderen met een paniekstoornis in vergelijking met een wachtlijstconditie is de eerste studie ter wereld. Helaas is de statistische power enigszins beperkt door de steekproefgrootte (n = 49), waardoor de conclusies met enige voorzichtigheid geinterpreteerd moeten worden. Een belangrijke tweede beperking is het ontbreken van een placebo-conditie

voor de paroxetineconditie en een steunende, structurerende interventiearm voor de CGT-conditie. Het feit dat beide actieve behandelingen vergelijkbare effect sizes lieten zien als die in eerder gepubliceerde meta-analyses bij (jong)volwassenen (Mitte, 2005), pleit tegen een grote invloed van een placebo-effect. Het gebruik van klachtenspecifieke zelfrapportagevragenlijsten die niet gevalideerd zijn bij ouderen met een paniekstoornis, is een volgende beperking. Hier kan overigens tegenin worden gebracht dat de beperkte empirische gegevens over het valideren van bestaande, voor (jong)volwassenen ontwikkelde klachtenspecifieke zelfrapportagevragenlijsten bij ouderen met een angststoornis niet tot bezwaren hebben geleid om zulke vragenlijsten ook bij ouderen te gebruiken (Crittendon et al., 2006, Fuentes et al., 2000). Tot slot hebben de bevindingen betrekking op een relatief jonge, relatief gezonde en mobiele groep ouderen (gemiddelde leeftijd is 69.6 jaar) Hierdoor zijn onze bevindingen niet generaliseerbaar naar meer kwetsbare en oudere ouderen.

De eerdergenoemde beperkingen die samenhangen met het gebruik van zelfrapportagevragenlijsten en de demografische kenmerken van de groep ouderen gelden ook voor de navolgende studies.

De studie naar verschillen in agorafobische cognities bij ouderen en (jong)volwassenen met een paniekstoornis met agorafobie (hoofdstuk 5) wordt vooral beperkt vanwege het feit dat er geen kwantitatieve analyse heeft plaatsgevonden naar agorafobische cognities die niet in de Agoraphobic Cognitions Questionnaire (ACQ) waren opgenomen.

Bij de vergelijking van CGT voor paniekstoornis met agorafobie bij ouderen en (jong) volwassenen (hoofdstuk 6) beinvloedt eveneens de beperkte omvang van de 60-plus steekproef ($n = 31$) de statistische power en dienen de conclusies met enige voorzichtigheid geinterpreteerd te worden. Daarnaast is niet uitgesloten dat er, in vergelijking met de groep (jong)volwassenen juist bij de groep ouderen sprake is van selectiebias, aangezien juist bij ouderen in grotere mate sprake is van onderdiagnostiek en onderbehandeling. Dit zou kunnen betekenen dat juist de ouderen met paniekstoornis die het best in staat zijn hun angst- en paniekklachten te verwoorden en te vertalen naar een duidelijke hulpvraag zijn verwezen naar onze gespecialiseerde polikliniek.

In hoofdstuk 7 wordt de relatie bestudeerd tussen leeftijd, ontstaansleeftijd en ziekteduur en het uiteindelijke behandelresultaat. Het operationaliseren van een vroege en late ontstaansleeftijd van de paniekstoornis is echter complex. Data uit epidemiologische en klinische studies definieren late ontstaansleeftijd meestal als het ontstaan boven het 30^{e} tot 50^{e} levensjaar (Katerndahl & Talamantes, 2000; Sheikh et al., 2004). Nadeel van zo'n lage leeftijdsgrens is het voorbijgaan aan de invloed van veroudering op de symptomatologie en ernst van de paniekstoornis. Aansluitend bij de algemeen geaccepteerde leeftijdsgrens van 55 tot 65 jaar en in navolging van andere onderzoekers (Segui et al., 2000) is besloten een klinische definitie te hanteren van 60 jaar en ouder voor een late ontstaansleeftijd. Daarnaast wordt het betrouwbaar vaststellen van de ontstaansleeftijd en de daarmee

samenhangende ziekteduur ongunstig beïnvloed omdat dit is gebaseerd op retrospectieve data. Het is mogelijk dat er sprake is van een differentieel effect van CGT en paroxetine bij ouderen met een paniekstoornis met agorafobie (hoofdstuk 8), waarbij CGT de voorkeur heeft bij ouderen met een late onstaansleeftijd en korte ziekteduur en farmacotherapie de voorkeursbehandeling zou kunnen zijn bij een jonge ontstaansleeftijd en een langdurig chronisch ziektebeloop. Omdat de bevindingen niet consistent significant zijn wanneer beide behandelingen in één analyse rechtstreeks met elkaar vergeleken worden en de onderzochte steekproef gering van omvang is, dient men de nodige terughoudendheid te betrachten bij deze conclusie.

Deze kritische reflectie op onze studies dient echter ook in de volgende context te worden geplaatst. Het rekruteren en includeren van ouderen voor wetenschappelijk onderzoek naar de behandeling van angststoornissen is wereldwijd nog steeds een moeizaam proces. Van de angststoornissen is alleen de behandeling van de gegeneraliseerde angststoornis bij ouderen relatief frequent onderzocht. Voor de andere angststoornissen zijn de empirische gegevens summier of ontbreken. De tot nu toe bekende factoren die hieraan ten grondslag liggen zijn eerder besproken. Binnen deze context is het een unicum dat voor de eerste maal CGT en SSRI-behandeling bij ouderen met een paniekstoornis gecontroleerd zijn onderzocht op effectiviteit, en dat voor de eerste maal de CGT voor paniekstoornis op effectiviteit is vergeleken binnen twee leeftijdsgroepen, namelijk een groep van 18-59 jaar en een groep van 60 jaar en ouder.

Conclusies en klinische betekenis

Samenvattend kan worden vastgesteld dat uit onze studies is gebleken dat enkel voor CGT voldoende empirisch bewijs in de hoogste bewijsklasse (meta-analyses) bestaat voor de behandeling van angststoornissen op hogere leeftijd. Dit betekent dat CGT de voorkeur verdient boven andere psychologische behandelvormen bij de behandeling van angststoornissen op oudere leeftijd. Hoewel eerder onderzoek suggereerde dat het bij ouderen met angststoornissen van belang is het CGT-protocol aan te passen om het resultaat van de behandeling te vergroten (Schuurmans, 2005) is het empirische fundament hiervoor bescheiden. Tot nu toe is er slechts één pilotstudie (n = 42; Mohlman et al., 2004) waaruit is gebleken dat een specifiek voor ouderen met gegeneraliseerde angststoornis (GAS) ontwikkeld CGT-protocol een beter resultaat heeft dan het standaard CGT-protocol voor GAS. Andere studies, groter van omvang en methodologisch van hogere kwaliteit, lieten geen verschil zien tussen een aan ouderen aangepast CGT-protocol en het standaard CGT-protocol voor GAS (Stanley et al., 2003a, Wetherell et al., 2003). Slechts één studie vond, in vergelijking met (jong)volwassenen, een lagere effect size voor CGT bij ouderen met angststoornissen (Schuurmans et al., 2006), terwijl de overige behandelresultaten van CGT voor ouderen met angststoornissen vergelijkbaar waren met

die bij (jong)volwassenen (hoofdstuk 2, dit proefschrift; Pinquart & Duberstein, 2007). Het is daarom nog te vroeg om te stellen dat bij ouderen met angststoornissen de CGT specifiek dient te worden aangepast aan de hogere leeftijd. Ook de suggestie dat ouderen met angststoornissen bij voorkeur met farmacotherapie dienen te worden behandeld (Pinquart & Duberstein, 2007) dient met enige terughoudendheid te worden betracht. Empirische gegevens over rechtstreekse vergelijkingen van CGT en farmacotherapie bij angststoornissen zijn er nauwelijks en voorts blijken de antidepressiva een vergelijkbaar risico te hebben op valongevallen en fracturen als de benzodiazepinen (o.a. Hartikainen et al., 2007).

De bevindingen van onze studies wezen vervolgens uit dat bij oudere patienten met een paniekstoornis met/zonder agorafobie zowel CGT als paroxetine effectief waren. Tevens was er een lichte voorkeur voor geprotocolleerde CGT wanneer de paniekstoornis was ontstaan op latere leeftijd. Beide behandelvormen werden goed verdragen op oudere leeftijd met slechts geringe uitval. Het is mogelijk dat het gegeven dat deze patienten verwezen waren naar een gespecialiseerde polikliniek een rol heeft gespeeld bij de geringe uitval (in vergelijking met andere studies op dit gebied) vanwege de aanwezige expertise betreffende de behandeling van angststoornissen. Omdat in deze setting ook systematisch veel aandacht werd besteed aan therapietrouwbevorderende interventies zou dit ook een aanvullende verklaring kunnen zijn voor de geringe uitval.

Tot slot was een belangrijke bevinding van onze studies dat leeftijd geen rol van betekenis speelde met betrekking tot het te behalen effect van de behandeling van paniekstoornis conform de bestaande richtlijnen. Eveneens waren de ontstaansleeftijd en ziekteduur geen voorspellers van een negatief behandelresultaat.

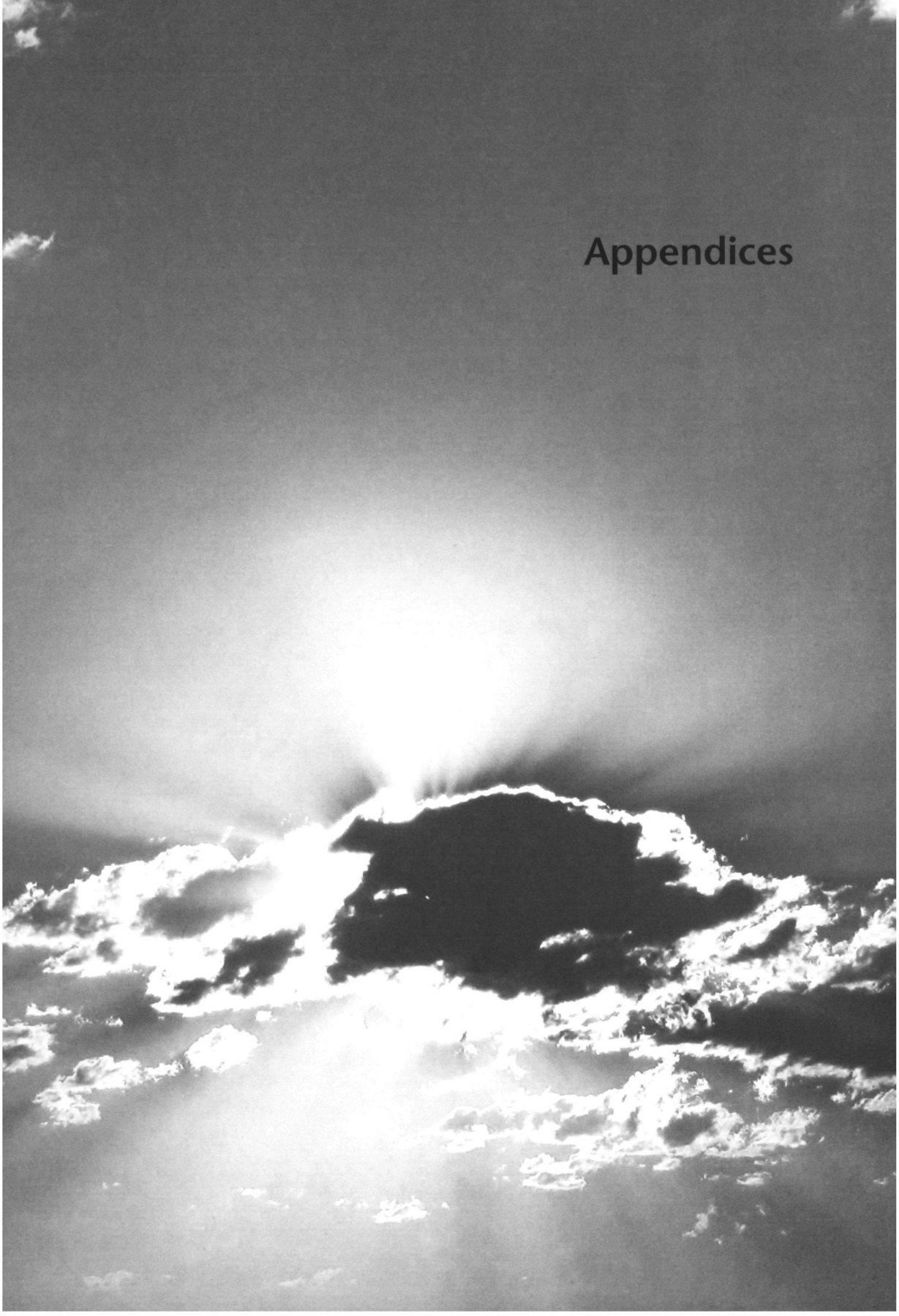
Aanbevelingen voor de klinische praktijk en toekomstig onderzoek

Van belang om nogmaals te noemen is dat ook onze steekproef relatief klein was en dat replicatie met een grotere steekproef, evenals onderzoek naar de overige angststoornissen op hogere leeftijd zeker nodig is vanwege de hoge prevalentie van deze aandoeningen in de oudere leeftijdscategorie (Kessler et al., 2005) en de hiermee gepaard gaande ziektelast (Wetherell et al., 2004). Op grond hiervan zouden wij de volgende, allerminst uitputtende, aanbevelingen willen doen:

1. Voorlichting aan verwijzers en patienten. Ondanks diverse inspanningen (o.a. berichtgeving in lokale dagbladen) om voldoende ouderen met angststoornissen verwezen te krijgen, was de instroom traag en het beloop van onze studie daardoor lang Het onderkennen van angststoornissen in de eerste lijn en het vervolgens gericht gaan behandelen blijft een belangrijk aandachtspunt. Gerichte voorlichting over angststoornissen bij ouderen voor zowel patienten zelf als verwijzers (meestal huisartsen) zou kunnen bijdragen tot verbetering van de herkenning en de behandeling van angststoornissen bij ouderen.

2. Het aanbieden van gespecialiseerde consultatiemogelijkheden in de huisartsenpraktijk. Veel ouderen ervaren, vanuit angst voor stigmatisering, een hoge drempel om doorverwezen te worden naar een GGZ-instelling. Gerichte screening door gespecialiseerde professionals binnen de voor ouderen veelal bekende en vertrouwde setting van de huisarts zou mogelijk deze drempel kunnen verlagen waardoor de mogelijkheden voor het aanbieden van gerichte behandeling zou kunnen worden vergroot.
3. Het opzetten van RCT's conform de bestaande richtlijnen voor de behandeling van specifieke angststoornissen met een drieledig doel:
   a Zijn ouderen met specifieke angststoornissen net zo effectief te behandelen conform de bestaande richtlijnen als (jong)volwassenen?
   b Indien dit niet het geval blijkt, welke zijn dan de variabelen die dit ongunstig beïnvloeden?
   c Zijn deze belemmerende variabelen met aanpassingen in de bestaande behandelprotocollen weg te nemen?
4. Het opzetten van prospectieve studies om na te gaan wat de effecten zijn van veroudering op de fenomenologie van de angststoornissen met als doel de diagnostiek en screening van angststoornissen bij ouderen te verbeteren.

Teneinde de kennis over de behandeling van angststoornissen bij deze specifieke doelgroep zo goed mogelijk naar voren te brengen, hebben wij naar aanleiding van ons onderzoek twee protocollen met betrekking tot de psychologische en farmacologische behandeling van angststoornissen op oudere leeftijd opgesteld voor de Cochrane Database of Systematic Reviews. Het doel is de huidige, beschikbare evidentie samen te vatten en periodiek aan te vullen met toekomstige empirische gegevens betreffende behandeling van angststoornissen op oudere leeftijd (zie bijlage A en B).



Appendices

Appendix A:
Cognitive-behavioural therapy for anxiety disorders in later life

Protocol information

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Appendix A has been published as:

Oude Voshaar RC, Hendriks GJ, Keijsers G, van Balkom AJ. Cognitive-behavioural therapy for anxiety disorders in later life [Protocol]. *Cochrane Database of Systematic Reviews*, 2009, Issue 1. Art. No.: CD007674. DOI: 10.1002/14651858.CD007674

Background

Description of the condition

Patients with anxiety complain of tension or restlessness, or they exhibit jitteriness, autonomic hyperactivity, vigilance, insomnia, distractibility, shortness of breath, numbness, apprehension, worry or rumination. Although most people experience such symptoms, an anxiety disorder is suspected when symptoms become disproportionately severe compared to their problems. According to the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM), anxiety disorders in later life are classified similarly to those in adult life and include panic disorder with and without agoraphobia, generalized anxiety disorder, social phobia, specific phobia, obsessive-compulsive disorder, and posttraumatic and acute stress disorder (APA 1980, APA 1987, APA 1994). Pure anxiety disorders in later life are rare, as most patients have a comorbid second anxiety disorder or depressive disorder (Flint,2005b; Kessler et al. 2005a; Lenze et al. 2005a; Van Balkom et al., 2000).

The prevalence rate of anxiety disorders among older adults living in the community has been estimated between 10 and 15%, with generalized anxiety disorder, panic disorder and specific phobias being the most common (Beekman et al., 1998; Kessler et al., 2005a). In later life, anxiety disorders impair quality of life by having a negative impact on functioning, well-being, and medical consumption (De Beurs et al., 1999; Van Zelst, De Beurs, Beekman, Van Dyck & Deeg, 2006; Wetherell et al , 2004a). Moreover, patients suffering from anxiety disorders have an increased risk of becoming depressed (Beekman et al., 2000), and left untreated, anxiety disorders tend to become chronic (Larkin, Copeland, Dewey, Davidson, Saunders, Sharma et al., 1992). In two large cohort studies, anxiety disorders in later life were prospectively associated with an increased mortality rate (Brenes et al., 2007; Van Hout et al., 2004).

Description of the intervention

First line treatment for anxiety disorders consists, of psychological treatment or antidepressant drugs (Trimbos-instituut, 2003; NICE, 2007) Community studies show that only 5.1% of older adults suffering from anxiety disorders receive psychological treatment and only 3.8% are prescribed an antidepressant drug (De Beurs et al., 1999). Both patient and physician characteristics may contribute to this phenomenon. Many older adults resist the use of antidepressants based on fear of dependence, prior negative experiences, resistance to viewing their symptoms as a medical illness, and concern that antidepressants will prevent natural feelings (Givens et al., 2006). The average duration between anxiety symptom onset and first treatment contact has been shown to be between 9 and 23 years, suggesting general practitioners do not easily recognize anxiety disorders (Kroenke, Spitzer, Williams, Monahan & Lowe, 2007; Wang et al., 2005a) The referral

rate from primary care to a mental health specialist is three times lower for older adults suffering from anxiety disorders (17%) compared to those suffering from depression (55%) (Ettner & Hermann, 1997). Furthermore, general practitioners themselves may be reluctant to prescribe drugs for anxiety symptoms being afraid for increased side effects in later life, for example the increased risk of falling and traffic accidents, memory impairment, and dependency associated with the use of benzodiazepines (Gorgels, Oude Voshaar, Mol, Breteler, Van de Lisdonk & Zitman, 2001) and hyponatraemia with the use of serotonin reuptake inhibitors (Wright & Schroeter, 2008). Also of concern are the adverse effects of drug interactions, such as gastrointestinal bleeding resulting from the concurrent use of serotonin reuptake inhibitors and non steroidal anti-inflammatory drugs in this age group known for polypharmacy use (Weinrieb et al., 2005; Yuan et al., 2006). As effective management of anxiety disorders in later life may improve outcome, it is important that guidelines for treatment become available.

Cognitive-behavioural therapy (CBT) combines principles of both behavioural and cognitive therapy. Cognitive therapy (CT) assumes that a patient's symptoms (e.g., anxiety) arise from misperceptions and attitudes about the world and themselves (Beck, 1995). Behavioural therapy (BT) is a directive, active approach involving principles of learning to help the patient develop new and adaptive ways of behaving (Bandura, 1969; Yates, 1970). As a psychotherapy, CBT is characterized as a structured, goal-oriented, problem-focused, time-limited intervention (Korrelboom & ten Broeke, 2004). In order to deal with age-associated cognitive impairment, some authors argue for inclusion of learning and memory aids like homework reminders, troubleshooting calls or weekly review of all concepts and techniques (Mohlman et al., 2003). Recent RCTs on older adults, however, remain inconclusive on whether age-related adaptations of psychotherapeutic techniques are necessary to remain efficacious for anxiety disorders in later life (Stanley et al., 2003a; Stanley et al., 2003b; Wetherell, Lenze & Stanley, 2005c).

How the intervention might work

CBT identifies habitual ways in which patients distort information (e.g., automatic thoughts) and teaches patients to identify and respond to their dysfunctional thoughts and beliefs, using a variety of techniques to change thinking, mood, and behaviour. Behavioural interventions help the patient develop new and adaptive ways of behaving. Exposure-based treatment utilizes gradual, systematic, repeated exposure to the feared object or situation to desensitize patients with anxiety disorders to the feared stimulus. The controlled exposures are predictable and the patient is taught a variety of adaptive coping strategies.

Why it is important to do this review?

CBT is generally considered the most effective psychotherapy for anxiety disorders (Trimbos-instituut, 2003) The efficacy of CBT for anxiety disorders in young and middle-aged adults is supported by a variety of meta-analyses (Bakker, Van Balkom, Spinhoven, Blaauw & Van Dyck, 1998, Furukawa et al , 2006, Mitte, 2005a, Mitte, 2005b, Westen & Morrison, 2001) However, whether these results also apply to older adults remains unclear since most trials exclude participants over the age of 65 years (Wetherell et al , 2003) Generalization of meta-analytic studies in young and middle-aged adults to older adults is limited, as older adults often have more chronic disorders, which are presumed to be more treatment resistant (Katz et al , 2002) Therefore, the current review aims to provide a comprehensive and up to date summary of the available evidence on CBT as a treatment for older adults Many of the earlier studies regarding the psychological treatment of anxiety disorders in later life suggest efficacy for CBT, but have been limited to subclinical anxiety and lack rigorous inclusion criteria, like the presence of an anxiety disorder according to diagnostic guidelines (Nordhus & Pallesen, 2003) Recent reviews generally conclude psychological treatment is effective for anxiety disorders in later life, but also conclude that there is a need for large, rigorous controlled trials for the different anxiety disorders (Ayers et al , 2007, Nordhus & Pallesen, 2003, Pinquart & Duberstein, 2007)

However, in later life, pure anxiety disorders are rare, as most patients have a comorbid second anxiety disorder or depressive disorder For the purposes of conducting the current review, therefore, generalized anxiety disorder, panic disorder with and without agoraphobia and social phobia, conditions that often overlap, will be combined into one single diagnostic category called anxiety disorders Obsessive-compulsive disorder and the stress disorders, acute and posttraumatic stress disorder, will be considered as separate diagnostic categories

Objectives

1 To assess the efficacy and feasibility of CBT (CT, BT, CBT and third wave CBT interventions) for different anxiety disorders in older adults aged 55 years or over compared with minimal management

2 To assess the efficacy and feasibility of CBT (CT, BT, CBT and third wave CBT interventions) for different anxiety disorders in older adults aged 55 years or over compared with other psychological therapies

3 To conduct a narrative review to additionally describe trials omitted from the quantitative analysis due to missing data

Methods

Criteria for considering studies for this review

Types of studies

All randomized controlled trials (RCTs) will be included. In the case of cross-over trials (a rare feature within this field of research), only the first randomization period will be included in the review. Studies using a quasi-randomized design will be excluded. Cluster RCTs, in which centres or therapists were randomized to intervention or control groups will be included, provided that the specific aim of the study was to examine the effect of the intervention.

Types of participants

All RCTs of older people (55 years or older) with a primary diagnosis of an anxiety disorder according to DSM-III (APA, 1980), DSM-III-R (APA, 1987), DSM-IV (APA, 1994), ICD-9 (ICD-9, 1979), ICD-10 (ICD-10, 1999) diagnostic criteria will be considered for inclusion, irrespective of culture and setting. The review will combine generalized anxiety disorder, panic disorder with and without agoraphobia and social phobia, conditions that often overlap, into one single category called anxiety disorders. Obsessive-compulsive disorder (OCD) and the stress disorders, acute and posttraumatic stress disorder, will be considered separately.

OCD is often hypothesized to be part of an obsessive-compulsive symptom spectrum, including body dysmorphic disorder, hypochondriasis, eating disorders, tic disorders and autism (Bartz & Hollander, 2006). Moreover, OCD is more treatment resistant compared to other anxiety disorders, and pharmacological treatments may be different from the other anxiety disorders, since they include the use of antipsychotics where there is treatment resistance and benzodiazepines are not effective agents (Bandelow, 2008; Trimbos-instituut, 2003). Posttraumatic stress disorder and acute stress disorder are reviewed and analyzed separately due to their causal relationship with psycho-traumatic events prior to the onset of the disorder. A similar distinction is made by the International Classification of Diseases (ICD-9, 1979; ICD-10, 1999), acknowledging four categories of anxiety disorders, namely 1) phobic anxiety disorders, 2) other anxiety disorders (together comparable to our category 'anxiety disorders'), 3) obsessive-compulsive disorders and 4) reaction to severe stress and adjustment disorders. For the purposes of this review, the three anxiety disorder categories (anxiety disorders, OCD and PTSD) will be stratified in analyses. Of studies that include both the target population and younger participants, the relevant data will be included on the condition that randomized age blocks have been used and data are reported in age blocks. Studies concerning anxiety symptoms that are part of the clinical presentation of another primary diagnosis (e.g. substance

use disorders, major depression) will be excluded, as well as studies involving patients with a comorbid psychiatric diagnosis of substance-related disorder, schizophrenia or psychotic disorder. However, studies involving participants with comorbid physical illnesses will be eligible for inclusion to increase generalizability, as most older people suffer from physical illnesses.

Types of interventions

Experimental intervention

Cognitive therapy (CT) is defined as cognitive restructuring of irrational and maladaptive anxiety beliefs. Behavioural therapy (BT) is defined as some form of exposure and/or relaxation exercises. Cognitive-behavioural therapy (CBT) is defined as delivering a combination of both CT and BT In studies where behavioural experiments are included, the therapy will be considered to be CBT, because behavioural experiments are exercises of new behaviour (BT) designed to challenge irrational or maladaptive beliefs (CT). Studies including third wave CBT interventions (e.g. mindfulness, acceptance and commitment therapy) will also be included. A minimum number of six therapy sessions has to be delivered, either in an individual or group format.

Comparator interventions

Non-CBT psychological therapies and minimal management will be included as control interventions. Non-CBT psychological therapies include non-directive (supportive) therapies, psychodynamic therapy and interpersonal psychotherapy. Minimal management (also sometimes described in trials as standard care, treatment as usual or waiting list), is defined as being elements of clinic attendance, investigation, reassurance, and simple advice, without explicit psychological therapy, and also may include naturalistic prescribing of medication and/or other interventions

Combination therapy

CBT in combination with pharmacological treatment will be excluded, as its superior effects over the monotherapies (Bakker et al., 1998; Van Balkom et al., 1997) have been challenged by recent meta-analyses (Furukawa et al., 2006; Mitte, 2005a; Mitte, 2005b).

Main comparisons

1. CBT, stratified as CBT, BT, CT and third wave CBT interventions versus minimal management.
2. CBT, stratified as CBT, BT, CT and third wave CBT interventions versus all non-CBT psychological therapies.

Types of outcome measures

Primary outcomes

The principal outcome used in this review will be anxiety, measured as follows:

1. Reduction in anxiety severity (continuous), measured by a well-validated, observer-rated instrument like the Hamilton Rating Scale for Anxiety (Hamilton, 1959), or if not available, a well-validated self-report instrument measuring general anxiety like the Beck Anxiety Inventory (Beck, 1988a). Validated disorder-specific instruments for obsessive-compulsive disorder or posttraumatic stress disorder will be used.
2. Clinical recovery or improvement (dichotomous), based on diagnostic interview or defined cut-off on validated scales, as specified by trial authors. In case the Clinical Global Impression scale [change item] (CGI-C) is used, responders are defined as having a change score of 1 = very much or 2 = much improved (Guy, 1976).

Secondary outcomes

The following secondary outcome measures will be included in the review.

1. Worrying, assessed continuously by well-validated, self-report questionnaires, like the Penn State Worrying Questionnaire (Meyer et al., 1990; Van Rijsoort, 1999).
2. Depression, assessed continuously by well-validated, self-report questionnaires, like the Beck Depression Inventory (Beck, 1988b).
3. Anxiety, assessed continuously by well-validated observer-rated or self-report questionnaires, in studies of obsessive-compulsive disorder or posttraumatic stress disorder.
4 Dropout rate will be included as a surrogate measure of feasibility of cognitive-behavioural therapy, in lieu of other more direct indicators of feasibility
5. Occurrence of adverse events.
6. Quality of life, assessed continuously by well-validated, self-report questionnaires, like the SF-36 (Ware & Sherbourne, 1992).

Search methods for identification of studies

A number of sources will be used to identify studies for possible inclusion in this review (see below). Studies will not be limited to any particular language

Electronic searches

The Cochrane Collaboration Depression, Anxiety and Neurosis Controlled Trials Register (CCDANCTR) will be searched using the following terms:

CCDANCTR-Studies

Diagnosis = Anxiety or Anxious or Phobi* or Panic or Obsess* or Compulsi* or Post-traumatic and Age-Group = Aged and Intervention = *Therapy

CCDANCTR-References

Keyword = Anxiety or Anxious or *phobi* or 'Panic Disorder' or 'Obsessive Compulsive Disorder' or 'Post-Traumatic Stress Disorders and Free-text = Elder* or Geriatri* or Senil* or Older or 'Old Age' or 'Late Life' or 'Aged, 80-And-Over'

A search of PubMed and of PsycINFO (which includes Dissertation Abstracts Internal, a database of unpublished dissertations) will also be conducted. The following keywords will be used: late-life, Elderly, Aged, Aged, 80 years and over, Old Age, Anxiety disorder, Anxiety, Panic, Agoraphobia, Phobia, Obsessive-compulsive, Posttraumatic, psychotherapy, cognitive therapy, behavior therapy, cognitive behavior therapy .

See Appendix 1 for the exact search strings that will be used in the different databases.

Searching other resources

Correspondence

Experts in this field and principal authors who have published controlled trials in the field of late-life anxiety will be asked if they know of any study which meets the inclusion criteria of this review.

Reference lists

Citation lists of potentially relevant papers obtained by these methods will be searched for further relevant trials, as will be the reference lists of those further relevant trials. In addition, the citation lists of relevant and recent systematic reviews were perused.

Data collection and analysis

Selection of studies

RCTs that have been identified will be independently assessed for inclusion by two review authors (RCOV & GJH), based on information included in the abstract and/or main body of the trial report. RCTs that both raters regard as satisfying the inclusion criteria specified in the 'Criteria for selecting studies' section will be collated by the raters (see above). If the raters disagree, the final rating will be made by consensus, if necessary with the involvement of another member of the review group (AJLMvB). Non-congruence in selection of trials will be reported as percentage disagreement. Considerable care will be taken to exclude duplicate publications.

Data extraction and management

Spreadsheet forms will be designed for the purpose of recording descriptive information, summary statistics of the outcome measures, the quality scale ratings, and associated commentary. These data will then be exported to RevMan. Where information is missing, the reviewers will contact investigators by letter or e-mail in an attempt to obtain it.

The following data will be extracted from each trial by two review authors independently (RCOV & GJH):

1. Description of the trials, including primary researcher and year of publication
2. Characteristics of the interventions, including the number of participants randomized to CBT-condition and control groups, therapycharacteristics, including the number of sessions provided, groups versus individual therapy, and components of the therapy (psycho-education, relaxation training, anxiety management, type(s) of exposure, cognitive techniques, and behavioural experiments), and finally the classification in CT, BT, CBT or third wave CBT interventions.
3. Characteristics of trial methodology, including the diagnostic and exclusion criteria employed, the screening instrument used, the inclusion of comorbidity, a minimal severity criterion, and the number of centres involved.
4. Characteristics of participants, including their gender distribution, mean age, and the duration of primary symptoms.
5. Outcome measures employed, and summary continuous (means and standard deviations) and dichotomous (number of responders) data. Additional information will be included, such as whether the data reflected the intent-to-treat (ITT) with either last observation carried forward (LOCF), or completer/observed cases (OC) sample, and the dropout rates of participants randomized to the experimental and control groups.

Assessment of risk of bias in included studies

Risk of bias will be assessed for each included study using the Cochrane Collaboration 'risk of bias' tool. The following six domains will be considered:

1. Sequence generation: Was the allocation sequence adequately generated?
2. Allocation concealment: Was allocation adequately concealed?
3. Blinding of participants, personnel and outcome assessors for each main outcome or class of outcomes: Was knowledge of the allocated intervention adequately prevented during the study?
4. Incomplete outcome data for each main outcome or class of outcomes: Were incomplete outcome data adequately addressed?
5. Selective outcome reporting: Are reports of the study free of suggestion of selective outcome reporting?
6. Other sources of bias: Was the study apparently free of other problems that could put it at a high risk of bias?

A description of what was reported to have happened in each study will be provided, and a judgement on the risk of bias will be made for each domain within and across studies, based on the following three categories:

A. Yes (low risk of bias).
B. Unclear.
C. No (high risk of bias).

Two independent review authors (RCOV & GJH) will assess the risk of bias in selected studies. Any disagreement will be discussed with a third review author (AJLMvB). Where necessary, the authors of the studies will be contacted for further information.

Measures of treatment effect

Dichotomous outcomes

These outcomes will be analyzed by calculating a pooled relative risk (RR) for each comparison, with 95% confidence intervals. Where overall results are significant, the number-needed-to-treat (NNT) to produce one outcome will be calculated.

Continuous outcomes

Anticipating different measures across studies, data will be pooled by calculating the standardized mean difference (SMD), using 95% confidence intervals.

Unit of analysis issues

Where studies have two relevant experimental conditions to be compared against a control condition, data will be managed as follows:

Continuous data – means, SDs and number of participants for each experimental condition will be pooled across the two conditions as a function of the number of participants in each condition (Law, Garrett & Nye; 2003) to be compared against the control condition.

Dichotomous data – active treatment groups will be collapsed into a single arm for comparison against the control group, or the control group will be split equally into two.

A similar approach will be used where studies have two relevant control conditions (e.g psychodynamic psychotherapy and a waiting-list control condition) to be compared against one experimental condition.

Dealing with missing data

Missing dichotomous data will be managed through intention to treat (ITT) analysis, in which it will be assumed that patients who dropped out after randomization had a negative outcome. Best / worse case scenarios will also be calculated for the clinical response outcome, in which it will be assumed that dropouts in the active treatment group had positive outcomes and those in the control group had negative outcomes (best case scenario), and that dropouts in the active treatment group had negative outcomes and those in the control group had positive outcomes (worst case scenario), thus providing boundaries for the observed treatment effect.

Missing continuous data will either be analyzed on an endpoint basis, including only participants with a final assessment, or analyzed using last observation carried forward to the final assessment (LOCF) if LOCF data were reported by the trial authors. Where SDs are missing, attempts will be made to obtain these data through contacting

trial authors Where SDs are not available from trial authors, they will be calculated from *t*-values, confidence intervals or standard errors, where reported in articles (Deeks, 1997a, Deeks, 1997b) If these additional figures are not available or obtainable, the study data will not be included in the comparison of interest

Assessment of heterogeneity

Statistical heterogeneity will be formally tested using the natural approximate chi-square test, which provides evidence of variation in effect estimates beyond that of chance Since the chi-square test has low power to assess heterogeneity where a small number of participants or trials are included, the *p*-value will be conservatively set at 0 1 Heterogeneity will also be tested using the I2 statistic, which calculates the percentage of variability due to heterogeneity rather than chance, with I2 values over 50% indicating strong heterogeneity (Higgins & Green, 2008)

Assessment of reporting biases

Where sufficient numbers of trials allow a meaningful presentation, funnel plots will be constructed to establish the potential influence of publication bias

Data synthesis

Data will be entered into RevMan 5 0 software by two review authors (double data entry) A fixed effect model will be used in the first instance to combine data If there is evidence of statistical heterogeneity, results will be recalculated using a random effects model, in order to obtain a more conservative estimate

Subgroup analysis and investigation of heterogeneity

Multiple subgroup analyses will be performed, but interpreted with caution, due to the risk of false positive conclusions If possible, the following subgroup analyses will be performed

1 Separate anxiety disorders (category 1), stratified as generalized anxiety disorder, panic disorder and social phobia
2 Minimal management control condition (waiting list versus other minimal management control conditions)
3 Other psychological therapy control conditions, stratified as psychodynamic, interpersonal and supportive therapies
4 CBT versus third wave CBT interventions
5 Group versus individual treatment delivery
6 The age classification of participants (55-79 years versus 80 years and over)

Where there are sufficient studies, these subgroup analyses will also be used to examine potential sources of clinical heterogeneity

Sensitivity analysis

Sensitivity analyses will also be undertaken to assess the degree to which the effect sizes depend on the assumptions made by the reviewers. Studies will be limited to those of higher quality as determined by risk of bias domains, including:

1. Allocation concealment.
2. Dropout rate lower than 20%.
3. Use of formal testing of fidelity to psychological therapy manual.
4. Use of blinded outcome assessors.

These sensitivity analyses will also be used to examine potential sources of methodological heterogeneity.

Acknowledgements

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Contributions of authors

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None of the authors do have competing interests. RCOV and GJH both have received an unconditional, educational grant from GlaxoSmithKline once. AJLMvB has received unconditional educational grants from Solvay Pharmaceuticals and GlaxoSmithKline.

Appendix

Search strategies

The following search strings will be used:

For the CCDANCTR-Studies database: Keyword = late-life OR Elderly OR Aged OR Old Age AND Keyword = Anxiety OR Panic OR Agoraphobia OR Phobia OR Obsessive-compulsive OR Posttraumatic AND Keyword = psychological therapy OR psychotherapy OR cognitive therapy OR behavio(u)r(al) therapy OR cognitive-behavio(u)r(al) therapy OR CBT

For PubMed: Keyword = Aged [MESH] OR Aged, 80 years and over [MESH] AND keyword = Anxiety disorder [MESH] AND Keyword = behaviour therapy [MESH]

For PsycINFO: Keyword = late-life OR Elderly OR Aged OR Old Age AND Keyword = Anxiety disorder [Thesaurus] AND Keyword = cognitive therapy [Thesaurus] or psychotherapy [thesaurus] OR cognitive behavior therapy [Thesaurus] OR behavior therapy [Thesaurus]

Appendix B: Pharmacotherapy for anxiety disorders in later life

Authors

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Appendix B has been published as:

Oude Voshaar RC, Hendriks GJ, Keijsers G, van Balkom AJ. Pharmacotherapy for anxiety disorders in later life (Protocol). *Cochrane Database of Systematic Reviews* 2009, Issue 2. Art. No.: CD007763. DOI: 10.1002/14651858.CD007763.

Text of review

Background:

Description of the condition

Patients with anxiety complain of tension or restlessness, or they exhibit jitteriness, autonomic hyperactivity, vigilance, insomnia, distractibility, shortness of breath, numbness, apprehension, worry or rumination. Although most people experience such symptoms, an anxiety disorder is suspected when symptoms become disproportionately severe compared to their problems. According to the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM), anxiety disorders in later life are classified similarly to those in adult life and include panic disorder with and without agoraphobia, generalized anxiety disorder, social phobia, specific phobia, obsessive-compulsive disorder, and posttraumatic and acute stress disorder (APA, 1980; APA, 1987; APA, 1994). Pure anxiety disorders in later life are rare, as most patients have a comorbid second anxiety disorder or depressive disorder (Flint, 2005b; Kessler et al., 2005a; Lenze et al., 2005a; Van Balkom et al., 2000).

The prevalence rate of anxiety disorders among older adults living in the community has been estimated between 10 and 15% (Beekman et al., 1998; Kessler et al., 2005a), with specific point prevalence for the distinct anxiety disorders of 7.3% for generalized anxiety disorder, 3.1% for social phobia, 1.0% for panic disorder with or without agoraphobia, 0.9% for posttraumatic stress disorder and 0.6% for obsessive-compulsive disorder (Beekman et al., 1998). In later life, anxiety disorders impair quality of life by having a negative impact on functioning and well-being and are associated with an increased health-care utilisation (De Beurs et al., 1999; Van Zelst et al., 2006; Wetherell et al., 2004a). Moreover, patients suffering from anxiety disorders have an increased risk of becoming depressed (Beekman et al., 2000), and left untreated, anxiety disorders tend to become chronic (Larkin et al., 1992). In two large cohort studies, anxiety disorders in later life were prospectively associated with an increased mortality rate (Van Hout et al., 2004; Brenes et al., 2007).

Description of the intervention

First line treatment for anxiety disorders consists of antidepressant drugs or psychological treatment (Trimbos-instituut, 2003; NICE, 2007). The place of benzodiazepines within the treatment of anxiety disorders differs between guidelines: some guidelines advise to never use benzodiazepines long-term (NICE, 2007), in some guideline benzodiazepines are a final treatment option when alternative strategies have failed (Trimbos-instituut,

2003) and some guidelines do not restrict the use of benzodiazepine but also do not give them a clear place (APA-guidelines). In the late nineties, community studies showed that only 3.8% of adults aged 55 years or over and suffering from anxiety disorders were prescribed an antidepressant, 25.8% were prescribed a benzodiazepine and 5.1% received psychological treatment (De Beurs et al , 1999). As no recent studies are available, it is unknown whether these figures have improved in the past decade. Both, patients and physician characteristics, may contribute to this phenomenon of undertreatment. Many older adults resist the use of antidepressants based on fear of dependence, prior negative experiences, resistance to viewing their symptoms as a medical illness, and concern that antidepressants will prevent natural feelings (Givens et al., 2006). The average duration between anxiety symptom onset and first treatment contact has been shown to be between 9 and 23 years, suggesting general practitioners do not easily recognize anxiety disorders (Wang et al., 2005; Kroenke et al., 2007). The referral rate from primary care to a mental health specialist is three times lower for older adults suffering from anxiety disorders (17%) compared to those suffering from depression (55%) (Ettner & Hermann, 1997). Furthermore, general practitioners themselves may be reluctant to prescribe drugs for anxiety symptoms in later life due to associated sideeffects that may become more pronounced in the elderly, for example the increased risk of falling and traffic accidents, memory impairment, and dependency associated with the use of benzodiazepines (Gorgels et al., 2001) and hyponatraemia with the use of serotonin reuptake inhibitors (Wright & Schroeter, 2008). Also of concern are the adverse effects of drug interactions, such as gastrointestinal bleeding resulting from the concurrent use of serotonin reuptake inhibitors and non steroidal anti-inflammatory drugs in this age group known for polypharmacy use (Yuan et al., 2006; Weinrieb et al , 2005).

How the interventions might work

Anxiety and fear symptoms are regulated by an amygdale-centered circuit. Worry, on the other hand, is regulated by a cortico-striatal-thalamic-cortical (CSTC) loop. These circuits may be involved in all anxiety disorders, with the different phenotypes reflecting not uniquely circuitry but rather divergent malfunctioning within those circuits. GABA is one of the key neurotransmitters involved in anxiety and in the anxiolytic action of many drugs used to treat anxiety disorders. Benzodiazepines act by enhancing the inhibitory actions of GABA at the level of the amygdala and the prefrontal cortex within the CSTC loops to relieve anxiety.

As the amygdala receives input from serotonergic neurons, which can have an inhibitory effect on some of its output, serotonergic agents may alleviate anxiety and fear by enhancing serotonin input to the amygdala Antidepressants that increase serotonin output by blocking the serotonin transporter are also effective in reducing symptoms of anxiety and fear. Such agents include selective serotonin reuptake inhibitors (SSRIs),

serotonin norepinephrine reuptake inhibitors (SNRIs) as well as tricyclic antidepressants (TCAs) A serotonin 1A partial agonist, buspirone, is recognized as a generalized anxiolytic In contrast to the direct action of benzodiazepines, the delayed onset of serotonergic agents suggest that these agents exert their therapeutic effects by virtue of adaptive neuronal events and receptor events rather than simply by the acute occupancy of associated receptors

Why it is important to do this review?

Meta-analyses of pharmacotherapy for anxiety disorders in young and middle-aged adults support the efficacy of pharmacotherapy (Abramowitz, 1997, Bakker et al , 2002, Fedoroff & Taylor, 2001, Mitte, 2005a, Mitte, 2005b, Stein et al , 2000, Van Balkom et al , 1997, Van der Linden et al , 2000) However, whether these results also apply to older adults remain unclear since most trials exclude participants over the age of 65 years (Wetherell et al , 2003) Generalization of these meta-analytic studies to older patients is limited as older adults often have more chronic disorders, which are presumed to be more treatment resistant (Katz et al , 2002), and have increased risk for adverse side effects due to age-associated changes in organ function and multimorbidity (Krasucki, Howard & Mann, 1999) Therefore, the current review aims to provide a comprehensive and up to date summary of the available evidence on pharmacotherapy as a treatment for older adults

Most of the earlier studies regarding the treatment of anxiety disorders in older people suggest efficacy for pharmacotherapy, but have been limited to uncontrolled comparisons and lack rigorous inclusion criteria, like the presence of an anxiety disorder according to diagnostic guidelines (e g Majercsik, Haller, Leveleki, Baranyi, Halsz & Rodgers, 2003, Small & Bystritsky, 1997, Wylie, Miller, Shear, Little, Mulsant, Pollock et al , 2000) A recent review concluded that SSRIs are efficacious for late-life anxiety disorders, whereas the effect of benzodiazepines and tricyclic agents did not reach significance, which might be explained by a lack of statistical power The authors concluded that there is a need for large, rigorous controlled trials for the different anxiety disorders (Pinquart & Duberstein, 2007), which was probably the reason that they included also uncontrolled trials and studies that failed to apply adequate psychiatric diagnoses by including patients with (only) subjective anxiety complaints

A final difficulty is the fact that in later life pure anxiety disorders are rare, as most patients have a comorbid second anxiety disorder or depressive disorder (Flint, 2005b, Lenze et al , 2001, Lenze et al , 2005a) For the purposes of conducting the current review, therefore, generalized anxiety disorder, panic disorder with or without agoraphobia and social phobia, conditions that often overlap, will be combined into one single diagnostic category called anxiety disorders Obsessive-compulsive disorder and the stress disorders, acute and posttraumatic disorder, will be considered as separate diagnostic categories

Objectives:

1. To assess the short- and long-term efficacy of different medication classes (benzodiazepines, selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), other medications) for different anxiety disorders in older adults aged 55 years or over compared with placebo.
2. To assess the relative efficacy of different medication classes for anxiety disorders in older adults aged 55 years or over
3. To assess adverse events associated with the use of each medication class, as well as comparing differences in the incidence of adverse events between different medication classes.
4. To conduct a narrative review to additionally describe trials omitted from the quantitative analysis due to missing data.

Criteria for selecting studies for this review:

Types of studies

All randomized controlled trials (RCTs) will be included. In the case of cross-over trials, only the first randomization period will be included in the review. Studies using a quasi-randomized design will be excluded. Cluster RCTs, in which centres were randomized to intervention or control groups will be included, provided that the specific aim of the study was to examine the effect of the intervention.

Types of participants

All RCTs of older people (55 years or older) with a primary diagnosis of an anxiety disorders according to DSM-III (APA, 1980), DSM-III-R (APA, 1987), DSM-IV (APA, 1994), ICD-9 (ICD-9, 1979), ICD-10 (ICD-10, 1999) diagnostic criteria will be considered for inclusion, irrespective of culture and setting.

The review will combine generalized anxiety disorder, panic disorder with and without agoraphobia and social phobia, conditions that often overlap, into one single category called anxiety disorders. Obsessive-compulsive disorder (OCD) and the stress disorders, acute and posttraumatic stress disorder, will be considered separately. OCD is often hypothesised to be part of an obsessive-compulsive symptom spectrum, including body dysmorphic disorder, hypochondriasis, eating disorders, tic disorders and autism (Bartz et al., 2006). Moreover, OCD is more treatment resistant compared to other anxiety disorders, and pharmacological treatments may be different from the other anxiety disorders, since they include the use of antipsychotics where there is treatment resistance

and benzodiazepines are not effective agents (Bandelow, 2008, Trimbos-instituut, 2003) Posttraumatic stress disorder and acute stress disorder are reviewed and analyzed separately due to their causal relationship with psycho-traumatic events prior to the onset of the disorder A similar distinction is made by the International Classification of Diseases (ICD-9, 1979, ICD-10, 1999), acknowledging four categories of anxiety disorders, namely 1) phobic anxiety disorders, 2) other anxiety disorders (together comparable to our category 'anxiety disorders'), 3) obsessive-compulsive disorders and 4) reaction to severe stress and adjustment disorders For the purposes of this review, the three anxiety disorder categories (anxiety disorders, OCD and PTSD) will be stratified in analyses

Of studies that include both the target population and younger participants, the relevant data will be included on the condition that randomized age blocks have been used and data are reported in age blocks

Studies concerning anxiety symptoms that are part of the clinical presentation of another primary diagnosis (e g substance use disorders, major depression) will be excluded, as well as studies involving patients with a comorbid psychiatric diagnosis of substance-related disorder, schizophrenia or psychotic disorder However, studies involving participants with comorbid physical illnesses will be eligible for inclusion to increase generalizability, as most older people suffer from physical illnesses

Types of interventions

Experimental and comparator interventions

All trials in which one or more medication classes are compared with a placebo Trials which include medications which do not fall within one of the 4 major classes (benzodiazepines, SSRIs, SNRIs, TCAs), such as buspirone and tranylcypromine, will also be included Where available, placebo-controlled dose comparison trials will also be included In this latter case, the different active intervention arms will be combined to one

Main comparisons

Each medication class (benzodiazepines, SSRIs, SNRIs, TCAs, other drugs) versus placebo (5 comparisons)

Each medication class against each of the other classes (10 comparisons)

The main comparisons will be evaluated for the end of treatment scores, or in case of repeated measures over a longer time-period, 12 weeks after the start of the intervention Follow-up results will be evaluated separately and are defined as outcome results between 6 and 12 months

Types of outcome measures

Primary outcomes

The principal outcome used in this review will be anxiety, measured as follows:

1. Clinical recovery or improvement (dichotomous), based on diagnostic interview or defined cut-off on validated scales, as specified by trial authors. In case the Clinical Global Impression scale [change item] (CGI-C) is used, responders are defined as having a change score of 1 = very much or 2 = much improved (Guy, 1976).
2. Reduction in anxiety severity (continuous), measured by a well-validated, observer-rated instrument like the Hamilton Rating Scale for Anxiety (Hamilton, 1959), or if not available, a well-validated self-report instrument measuring general anxiety like the Beck Anxiety Inventory (Beck, 1988a). These scales are potentially able to determine whether the core features of late-life anxiety disorders respond to medication (rather than simply the comorbid symptoms). Validated disorder-specific instruments for obsessive-compulsive disorder or posttraumatic stress disorder will be used.
3. Occurrence and number of adverse events as reported by the trial authors.

Secondary outcomes

The following secondary outcome measures will be included in the review:

1. Worrying, assessed continuously by well-validated, self-report questionnaires, like the Penn State Worrying Questionnaire (Meyer et al., 1990; Van Rijsoort, 1999).
2. Depression, assessed continuously by well-validated, self-report questionnaires, like the Beck Depression Inventory (Beck, 1988b).
3. Anxiety, assessed continuously by well-validated observer-rated or self-report questionnaires, in studies of obsessive-compulsive disorder or posttraumatic stress disorder.
4. Dropout rate will be included as a surrogate measure of tolerance of the different medication classes.
5. Quality of life, assessed continuously by well-validated, self-report questionnaires, like the SF-36 (Ware & Sherbourne, 1992).

Search methods for identification of studies

A number of sources will be used to identify studies for possible inclusion in this review (see below). Studies will not be limited to any particular language.

Electronic searches

A search of the Cochrane Collaboration Depression, Anxiety and Neurosis Controlled Trials Register (CCDANCTR), PubMed and PsycINFO (which includes Dissertation Abstracts Internal, a database of unpublished dissertations) will be conducted We will use detailed search strategies for each database searched, which will be adapted for each database to take account of differences in controlled vocabulary and syntax rules (see appendix 1). The used search terms are: Anxiety, Anxiety disorder, Anxious, Phobia, Panic disorder, Obsessive Compulsive Disorder, Post-traumatic Stress Disorders, Aged, Aged, 80-years-And-Over, Old Age, Elderly, Geriatric, Senil, Older, Late Life, Antidepressive Agents, Monoamine Oxidase Inhibitors, Selective Serotonin Reuptake Inhibitors, Tricyclic Drugs, Anti-Anxiety Agents, Benzodiazepines. The searches will be extended with the names of individual drugs.

Searching other resources

Correspondence

Pharmaceutical companies and experts in this field (including all authors who have published controlled trials in the field of late-life anxiety) will be asked if they know of any study that examines the efficacy of pharmacological strategies for the treatment of anxiety disorders in later life. Furthermore, clinical trials registries, as the WHO portal and controlled-trials.com, will be consulted.

Reference lists

Citation lists of potentially relevant papers obtained by these methods will be searched for further relevant trials, as will be the reference lists of those further relevant trials. In addition, the citation lists of relevant and recent systematic reviews were perused

Data collection and analysis

Selection of studies

RCTs that have been identified will be independently assessed for inclusion by 2 review authors (GJH & GK), based on information included in the abstract and/or main body of the trial report. RCTs that both raters regard as satisfying the inclusion criteria specified in the 'Criteria for selecting studies' section will be collated by the raters (see above). If the raters disagree, the final rating will be made by consensus, if necessary with the involvement of another member of the review group (RCOV). Non-congruence in selection of trials will be reported as percentage disagreement. Considerable care will be taken to exclude duplicate publications.

Data extraction and management

Spreadsheet forms will be designed for the purpose of recording descriptive information, summary statistics of the outcome measures, the quality scale ratings, and associated commentary. This data will then be exported to RevMan. Where information is missing, the reviewers will contact investigators by e-mail in an attempt to obtain it.

The following data will be extracted from each trial by two review authors independently (GJH & GK):

1. Description of the trials, including primary researcher and year of publication
2. Setting in which the trial is conducted (primary care, secondary care, academic/ specialized anxiety clinic).
3. Characteristics of the interventions, including the number of participants randomized to the medication and control groups, the name of the medication, the class to which it belongs (benzodiazepines, SSRIs, SNRIs, TCAs, other), the dosages used and the duration of medication usage.
4. Characteristics of trial methodology, including the diagnostic and exclusion criteria employed, the screening instrument used, the inclusion of comorbidity (especially the allowance of a comorbid diagnosis of major depression), the use of a placebo run-in, a minimal severity criterion, the number of centres involved, duration of follow-up.
5. Characteristics of participants, including their gender distribution, mean age, and the duration of primary symptoms.
6. Outcome measures employed, and summary of dichotomous (number of responders) and continuous (means and standard deviations) data at end of treatment (6 through 16 weeks) and at follow-up (6 through 12 months). Additional information will be included, such as whether the data reflected the intent-to-treat (ITT) with either last observation carried forward (LOCF), or completer/observed cases (OC) sample, the number of participants experiencing serious adverse events (SAEs), and the dropout rates of participants randomized to the medication and control groups.

Assessment of risk of bias in included studies

Risk of bias will be assessed for each included study using the Cochrane Collaboration 'risk of bias' tool. The following six domains will be considered:

1. Sequence generation: Was the allocation sequence adequately generated?
2. Allocation concealment: Was allocation adequately concealed?
3. Blinding of participants, personnel and outcome assessors for each main outcome or class of outcomes: Was knowledge of the allocated intervention adequately prevented during the study?

4. Incomplete outcome data for each main outcome or class of outcomes: Were incomplete outcome data adequately addressed?
5. Selective outcome reporting: Are reports of the study free of suggestion of selective outcome reporting?
6. Other sources of bias: Was the study apparently free of other problems that could put it at a high risk of bias?

A description of what was reported to have happened in each study will be provided, and a judgement on the risk of bias will be made for each domain within and across studies, based on the following three categories:

A. Yes (low risk of bias).
B Unclear.
C. No (high risk of bias).

Two independent review authors (GJH & GK) will assess the risk of bias in selected studies. Any disagreement will be discussed with a third review author (RCOV). Where necessary, the authors of the studies will be contacted for further information.

Measures of treatment effect

Dichotomous outcomes

These outcomes will be analyzed by calculating a pooled relative risk (RR) for each comparison, with 95% confidence intervals. Where overall results are significant, the number-needed-to-treat (NNT) to produce one outcome will be calculated.

Continuous outcomes

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Unit of analysis issues

Studies comparing two experimental conditions consisting of the same drug in different dosages or consisting of two drugs from the same class to a control condition, data will be managed as follows:

- Dichotomous data – active treatment groups will be collapsed into a single arm for comparison against the control group, or the control group will be split equally into two.
- Continuous data – means, SDs and number of participants for each experimental condition will be pooled across the two conditions as a function of the number of participants in each condition (Law et al., 2003) to be compared against the control condition.

In case of two different experimental conditions being evaluated against placebo, both experimental conditions will be included in (different) meta-analyses against the same placebo condition

Dealing with missing data

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2. The age classification of participants (55-79 years versus 80 years and over).
3. Duration of treatment (less than 12 weeks versus 12 weeks and over).
4. Presence or absence of major depression.

Where there are sufficient studies, these subgroup analyses will also be used to examine potential sources of clinical heterogeneity.

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Sensitivity analyses will also be undertaken to assess the degree to which the effect sizes depend on the assumptions made by the reviewers. Studies will be limited to those of higher quality as determined by risk of bias domains, including:

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3. Use of clinician rated scales.
4. Use of blinded outcome assessors.

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Search strategy

The following search strings will be used:

For studies included in the Cochrane Collaboration Depression, Anxiety and Neurosis Controlled Trials Register (CCDANCTR):
Diagnosis = Anxiety or Anxious or Phobi* or Panic or Obsess* or Compulsi* or Post-Traumatic
AND
Age-Group = Aged
AND
Intervention = Antidepressive Agents or 'Monoamine Oxidase Inhibitors' or 'Selective Serotonin Reuptake Inhibitors' or 'Tricyclic Drugs' or 'Benzodiazepines' (extended with the names of individual drugs)

For studies included in the CCDANCTR-References :
Keyword = Anxiety or Anxious or *phobi* or 'Panic Disorder' or 'Obsessive Compulsive Disorder' or 'Post-Traumatic Stress Disorders
AND
Free-text = Elder* or Geriatri* or Senil* or Older or 'Old Age' or 'Late Life' or 'Aged, 80-And-Over'

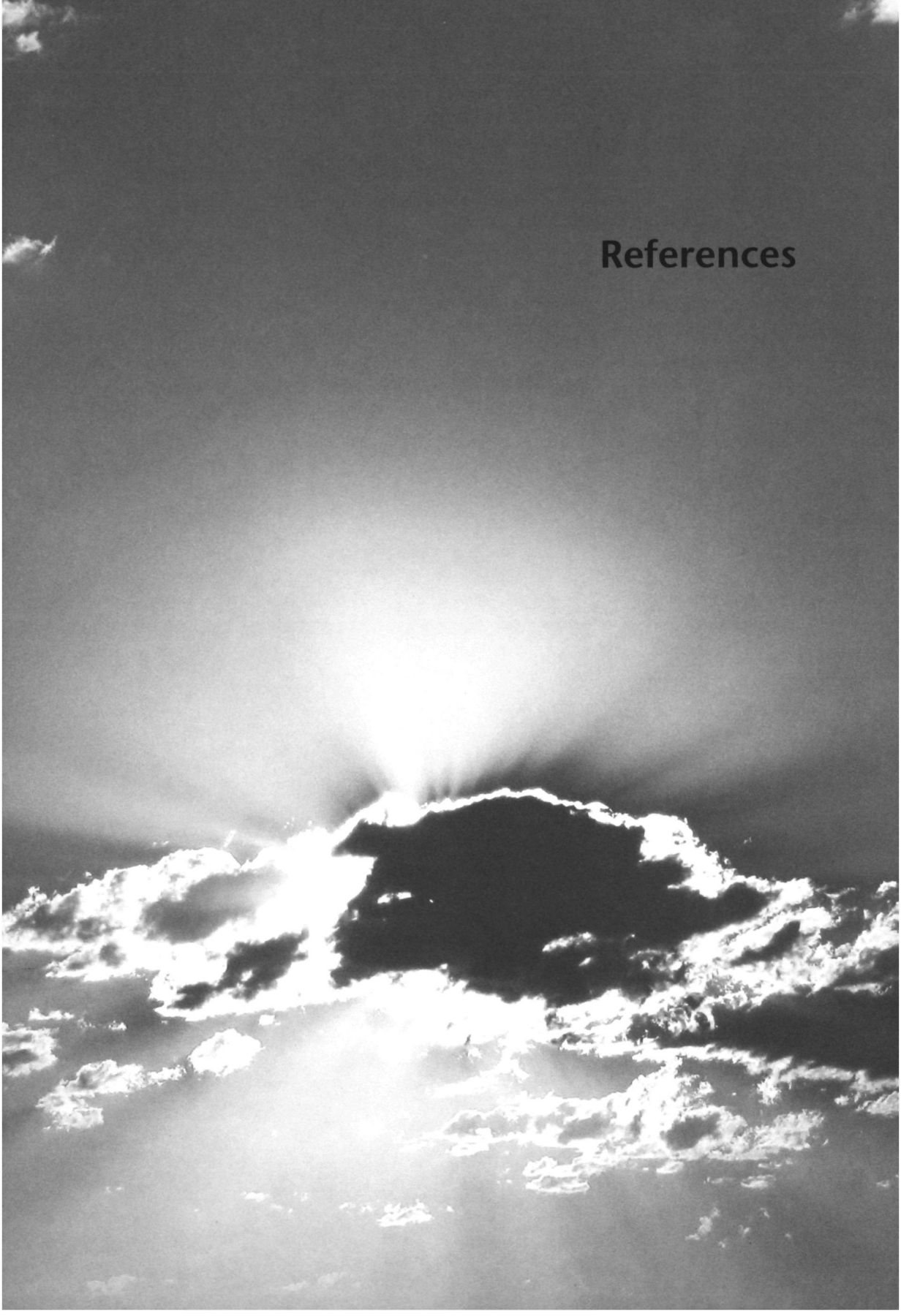
For the CCDANCTR-Studies database:
Keyword = late-life OR Elderly OR Aged OR Old Age
AND
Keyword = Anxiety OR Anxious OR Panic OR Phobi* OR Obses* OR Compulsi* OR Post-Traumatic
AND
Keyword = Antidepressant Agents OR Anti-Anxiety Agents.

For PubMed:
Keyword = Aged [MESH] OR Aged, 80 years and over [MESH]
AND
keyword = Anxiety disorder [MESH]
AND
Keyword = Antidepressant agents [MESH] OR Anti-anxiety agents [MESH].

For PsycINFO:
Keyword = late-life OR Elderly OR Aged OR Old Age

AND
Keyword = Anxiety disorder [Thesaurus]
AND
Keyword = antidepressant agents [thesaurus] OR anti-anxiety agents [Thesaurus]

These search strings will be extended with the names of the individual drugs: Acetylcarnitine or Alaproclate or Amersergide or Amiflamine or Amineptine or Amitriptyline or Amoxapine or Befloxatone or Benactyzine or Brofaromine or Bupropion or Butriptyline or Caroxazone or Chlorpoxiten or Cilosamine or Cimoxatone or Citalopram or Clomipramine or Clorgyline or Clorimipramine or Clovoxamine or Deanol or Demexiptiline or Deprenyl or Desipramine or Dibenzipin or Diclofensine or Dothiepin or Doxepin or Duloxetine or Etoperidone or Femoxetine or Fluotracen or Fluoxetine or Fluparoxan or Fluvoxamine or Idazoxan or Imipramine or Iprindole or Iproniazid or isocarboxazid or Litoxetine or Lofepramine or Maprotiline or Medifoxamine or Melitracen or Metapramine or Mianserin or Milnacipran or Minaprine or Mirtazapine or Moclobemide or Nefazodone or Nialamide or Nomifensine or Nortriptyline or Noxiptiline or Opipramol or Oxaflozane or Oxaprotiline or Pargyline or Paroxetine or Phenelzine or Piribedil or Pirlindole or Pivagabine or Prosulpride or Protriptyline or Quinupramine or Reboxetine or Rolipram or Sertraline or Setiptiline or Teniloxine or Tetrindole or Thiazesim or Thozalinone or Tianeptine or Toloxatone or Tomoxetine or Tranylcypromine or Trazodone or Trimipramine or Venlafaxine or Viloxazine or Viqualine or Zimeldine or benzodiazepine* or Adinazolam or Alprazolam or Bentazepam or Bromazepam or Brotizolam or Camazepam or Chlordiazepoxide or Cinolazepam or Clobazam or Clonazepam or Clorazepate or Clotiazepam or Cloxazolam or Delorazepam or Diazepam or Estazolam or Etizolam or Fludiazepam or Flunitrazepam or Flurazepam or Flutoprazepam or Halazepam or Haloxazolam or Ketazolam or Loprazolam or Lorazepam or Lormetazepam or Medazepam or Metaclazepam or Mexazolam or Midazolam or Nimetazepam or Nitrazepam or Nordazepam or Oxazepam or Oxazolam or Pinazepam or Prazepam or Quazepam or Temazepam or Tetrazepam or Tofisopam or Triazolam or Zolazepam or Zaleplon or Zolpidem or Zopiclone.



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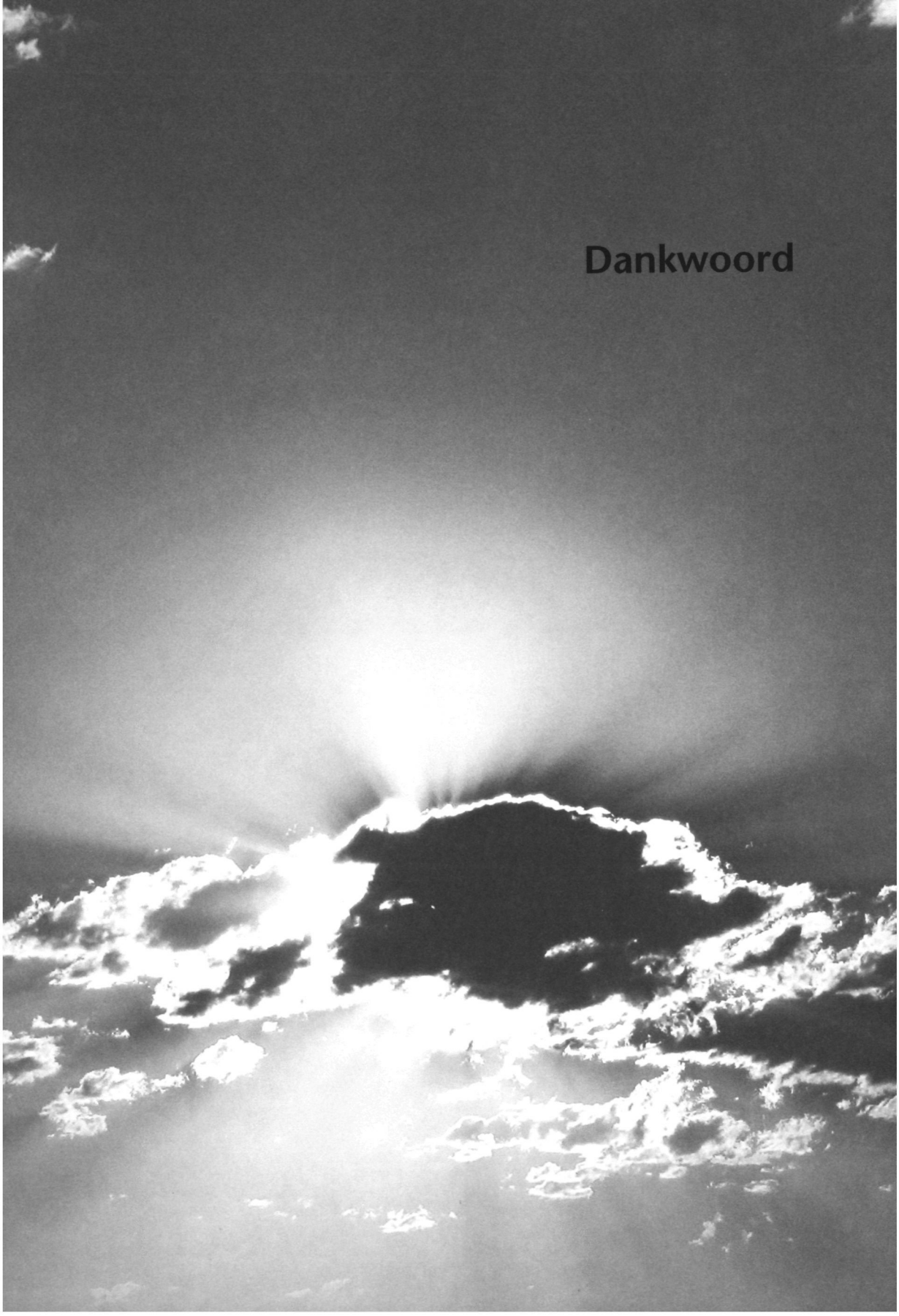


Dankwoord

Eindelijk is het dan zover. Mijn proefschrift is geschreven, waarmee ik, althans volgens de definities, heb laten zien in staat te zijn zelfstandig onderzoek te doen en dit fatsoenlijk en leesbaar te beschrijven. Dat zelfstandig onderzoek een rekbaar en relatief begrip is, zult u hierna kunnen lezen.

Dit proefschrift was nooit tot stand gekomen als ik daarbij niet de ondersteuning had gehad van velen die ik hierbij wil bedanken.

Kees Hoogduin wil ik bedanken voor het gestelde vertrouwen toen hij in 1998 zonder meer instemde om als promotor betrokken te zijn bij mijn onderzoek. Kees, zonder jouw bijdrage was dit project niet van de grond gekomen. Van tijd tot tijd beteugelde je mijn optimistische inslag. Het heeft me geholpen om door te kunnen blijven zetten en het heeft me een passende wetenschappelijke bescheidenheid bijgebracht. In de eindfase, toen het schrijven van dit proefschrift stagneerde, heb je me daar op orthodox gedragstherapeutische wijze doorheen geloodst met stevige 'sancerre'-sancties als ik deadlines zou overschrijden Hoe het vak van psychiater beoefend dient te worden in praktiserend, onderwijskundig en wetenschappelijk opzicht heb ik van jou geleerd. Het was, en is nog steeds, voor mij een genoegen dat ik de kunst af heb mogen kijken en dat we nog steeds samenwerken in het 'angstpoli-team' met een aantal van je promovendi.

Mijn copromotores, Ger Keijsers en Richard Oude Voshaar, waren mijn vaste begeleiders. Ger, samen hebben we aan de wieg gestaan van dit project en je bent er vanaf de voorbereiding in 1998 non-stop bij betrokken geweest. Ik wil je bedanken voor je inzet in de afgelopen jaren en vooral ook dat je nooit getwijfeld hebt aan de 'goede afloop' Je kritische, gedetailleerde en zorgvuldige becommentariering van de stukken die ik aanleverde, was zeer leerzaam en heb ik altijd bijzonder gewaardeerd. De manuscripten werden er beduidend beter van. Heel plezierig was dat je ook in de eindfase van mijn schrijfproces, toen er de nodige tijdsdruk lag, scherp en snel commentaar leverde. Het werk is gedaan, maar het begeleiden is overgegaan naar samenwerken in het Nijmegen Centre for Anxiety Research and Expertise (Nij-CARE), met van tijd tot tijd gezellige etentjes. Ik verheug me op het voortzetten daarvan! Richard, voor mij ben je op het juiste moment ingestapt bij dit project. Je specifieke kennis van de ouderenpsychiatrie gaf me de gelegenheid om met je te debatteren over de verschillende thema's en vraagstellingen van dit project. Het is heel waardevol geweest bij het analyseproces en het aanscherpen van de manuscripten. Ik heb met verbazing en enige afgunst aanschouwd met welk een energie en tempo je hierin opereerde. Veel dank hiervoor, en niet in de laatste plaats voor de tijd die je ook privé hebt genomen om aan het door mij gewenste tempo tegemoet te komen. Ook wij zetten de samenwerking voort binnen de polikliniek Mentalis van de afdeling ouderenpsychiatrie van GGz-Nijmegen. Wie weet slagen we erin de Gelderse zorglijn angststoornissen van Pro Persona uit te breiden met een heus zorg- en onderzoeksprogramma voor oudere mensen met angststoornissen.

Mirjam Kampman wil ik hartelijk danken voor haar rol als coordinator bij dit project,

het begeleiden en supervíseren van de therapeuten, de ondersteuning bij de analyse en het voor mij waarnemen tijdens afwezigheid. Je loyaliteit, inzet en steun waren vanzelfsprekend. Dat heb ik enorm gewaardeerd.

Theo Broekman was als methodoloog-statisticus bij het project betrokken. Theo, ik wil je bedanken voor het maken van de onderzoeksdossiers, het bouwen van de database, je wetenschappelijke rechtlijnigheid en kennis van onder andere de 'mixed models'. In een tijdgeest waarin veel druk op wetenschappelijk scoren wordt gelegd, houd jij je rug kaarsrecht. We hebben daar de nodige discussies over gevoerd en ik heb er veel van geleerd. Maar nu is het tijd om te tennissen en zijn de rollen omgekeerd!

Marc Verbraak wil ik bedanken voor zijn deelname aan de begeleidingsgroep. Je hebt een belangrijke rol vervuld bij de supervisie en begeleiding van onder andere de therapeuten die bij dit project betrokken waren en ze te ondersteunen om stevig aan de protocollaire behandellijn vast te blijven houden. Het kan geen toeval zijn dat ook wij weer bezig zijn een samenwerkingsverband op te zetten. Welkom terug bij Nij-CARE. Als oud-medewerker van HSK vind ik het verheugend dat we de banden aantrekken.

Jaap Couvée was verantwoordelijk voor de toekenning van de onvoorwaardelijke subsidie vanuit GlaxoSmithKline. Deze subsidie heeft in belangrijke mate bijgedragen aan het financieel mogelijk maken van dit project, waarvoor hartelijk dank.

Een onderzoeksproject als dit had niet uitgevoerd kunnen worden zonder de onvoorwaardelijke steun van mijn 'angstpoli-team'. Zonder de voormalige medewerkers tekort te willen doen, wil ik toch enkelen persoonlijk bedanken. Esther Allart, Judith van Bueren, Marcel van den Ende, Bram Klaassen, Agnes van Minnen, Wilbert Pieterse en Mirjam van Rees, jullie vormden de 'kern' van de angstpoli. Door jullie onderlinge cohesie en zelfsturende kwaliteiten hebben jullie mij in de gelegenheid gesteld om mij op dit project te concentreren en het tot een goed einde te brengen. Roos Janssens en Angie Leijsner wil ik in het bijzonder bedanken voor het invoeren van een deel van de data. Alle voormalige en huidige gz-psychologen in opleiding, die als therapeut bij dit project betrokken waren, ben ik dankbaar voor hun inzet en zorg ten behoeve van de patienten die in het kader van dit onderzoek zijn behandeld.

Vier studenten klinische psychologie, Miranda van den Boom, Maartje van Heijkoop, Janina Kempkes en Sarah Lebhar, die hun doctoraalscriptie hebben geschreven over delen van dit onderzoeksproject ben ik dankbaar voor het volledig invoeren van de onderzoeksgegevens. Het heeft het analyseren van de data en het afronden van het proefschrift gefaciliteerd

Hanneke Meulenbroek dank ik voor de vakkundige wijze waarop de teksten op grammaticale onjuistheden en taal- en stijlfouten zijn gecorrigeerd. Hanneke, ik heb de samenwerking altijd als uitermate plezierig en behulpzaam ervaren!

De medewerkers van het Centrum voor Angststoornissen Overwaal (de voormalige Kliniek Overwaal, angstpoli GGz-Nijmegen en Focus) ben ik in het bijzonder dankbaar.

Terwijl er zich allerlei veranderingen gingen voltrekken, hebben jullie mij als kersverse directeur de ruimte gegeven om het proefschrift af te ronden. Zonder de anderen tekort te doen wil ik in dit verband enkelen noemen: Noud Bekkers, Hanneke van de Logt, Boris van Passel, Lieske Sonnenveldt, Esther Vermeulen, Yvon van de Weegen en Anja de Weerd. Ik heb jullie extra werk bezorgd, bedankt voor jullie support.

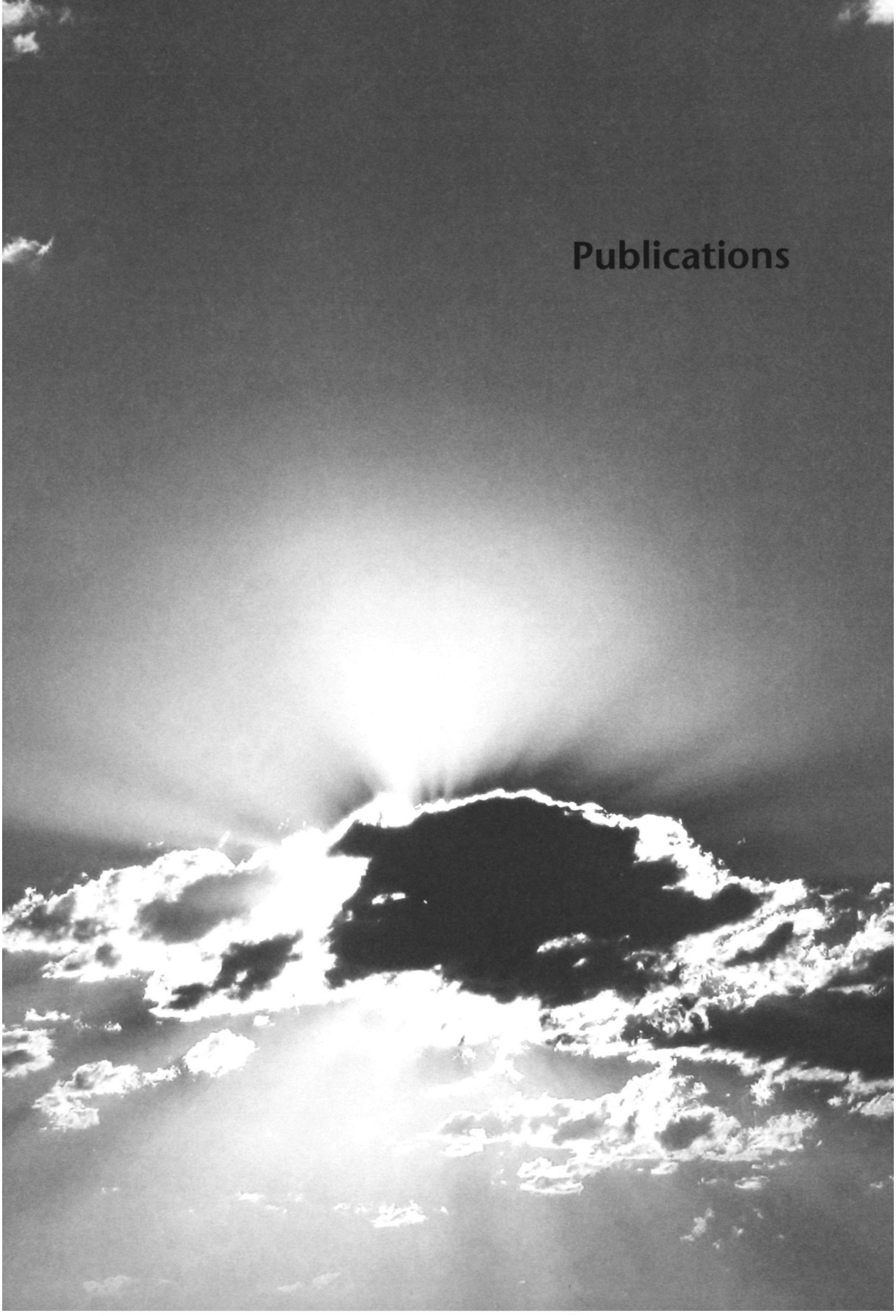
Mijn compagnon Jim Roosenboom en de medewerkers van Hendriks & Roosenboom ben ik in het bijzonder dankbaar omdat zij mij in een periode dat het bedrijf sterk groeide de ruimte gaven het schrijfproces te voltooien. Daarnaast was er financiele ondersteuning voor de statistische analyse. Hartelijk dank daarvoor.

Alle patienten die bereid zijn geweest om aan het onderzoeksproject deel te nemen, wil ik bedanken voor het gestelde vertrouwen in ons team, voor hun bereidwilligheid om alle vragenlijsten in te vullen, maar vooral ook omdat ze de stap hebben durven zetten om in behandeling te komen. De resultaten van dit onderzoeksproject hebben laten zien dat het niet voor niets is geweest!

Het bestuur van Forum GGz-Nijmegen, Jos Poelmann en Ron Sponselee, dank ik voor hun bijdrage om het proefschrift te kunnen drukken, en voor het gestelde vertrouwen om mij juist in deze eindfase van het afronden van mijn proefschrift toch te benoemen als directeur van Overwaal. Dat was een tamelijk risicovolle 'belegging'. Ik hoop dat het rendement dan ook naar behoren is.

Robert-Jan en Evert, jullie zijn mijn paranimfen en het heeft even geduurd voordat jullie in actie konden komen. Veel dank voor jullie geduld en betrokkenheid. Vooral de laatste drie jaar zijn bijzonder intensief geweest. Ik heb jullie gemist, dat gaan we inhalen.

Mijn familie en vrienden wil ik eveneens bedanken voor hun steun en geduld.
Het proefschrift draag ik op aan mijn vader en moeder. Lieve ma en pa, bedankt voor jullie onvoorwaardelijke steun en liefde.
Als laatste in een lange rij, lieve Petra, sluit ik mijn dankwoord af bij jou. Het in woorden uitdrukking geven aan wat jij voor mij betekende in dit proces dekt bij lange na niet de lading. Laat ik er dit over zeggen. Je bent voor mij de belangrijkste en allerliefste, ook dit is ons gelukt! We zijn een ijzersterk team, en dat blijven we nog heel lang! En de camper, die laten we niet meer wachten.



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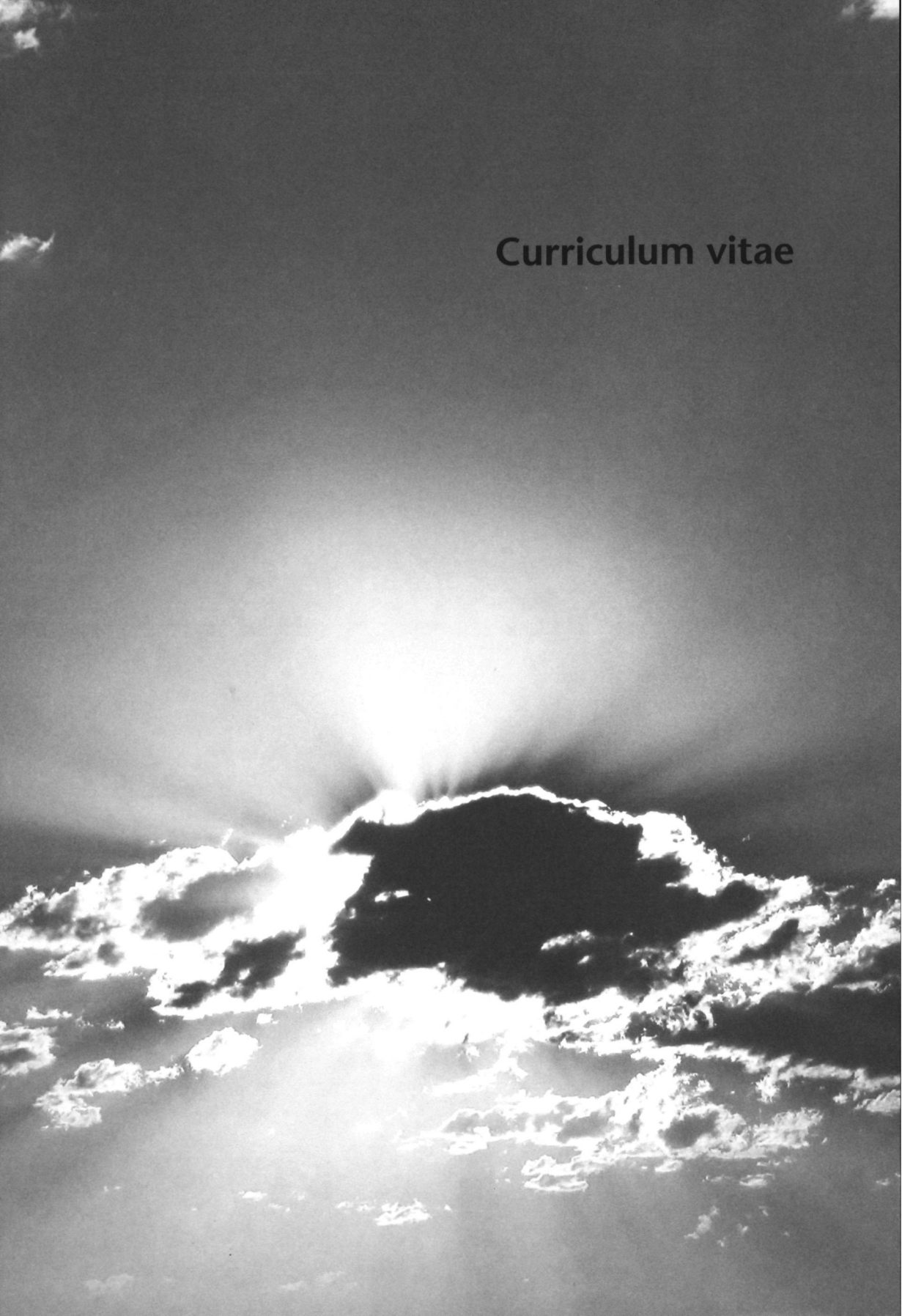

Curriculum vitae

Gert-Jan Hendriks werd geboren op 23 april 1960 in Elst (Gld.). In 1978 behaalde hij het atheneum-β-diploma aan het Katholiek Gelders Lyceum te Arnhem. Na een jaar psychologie te hebben gestudeerd aan de Radboud Universiteit Nijmegen (RU), volgde de studie geneeskunde aan dezelfde universiteit. Het artsendiploma werd behaald in 1988. Na tot 1990 werkzaam te zijn geweest als basisarts volgde hij tot 1995 de opleiding tot psychiater binnen het opleidingsconsortium Oost-Nederland bij het toenmalig psychiatrisch ziekenhuis Wolfheze. Van 1994 tot 1996 was hij voorzitter van de Landelijke Vereniging Assistent-Geneeskundigen (LVAG) en afgevaardigd bestuurslid bij de Landelijke vereniging van Artsen in Dienstverband (LAD). Hij werkte van 1995 tot 1998 als psychiater bij de afdeling psychiatrie van het Universitair Medisch Centrum 'St. Radboud' te Nijmegen en van 1995 tot 1999 als consulent-psychiater bij de HSK Groep Van 1998 tot 2008 was hij als teamleider/psychiater verbonden aan de angstpolikliniek van GGz-Nijmegen. In deze periode was hij tot 2006 consulent-psychiater bij het ambulatorium volwassenen van het Academisch Centrum Sociale Wetenschappen van de RU Nijmegen. Daarnaast vestigde hij zich in 1999, samen met Jim Roosenboom, als parttime vrijgevestigd psychiater in Velp (Gld.). De praktijk verhuisde in 2002 naar Arnhem en in 2006 richtten zij het Zelfstandig Behandel Centrum (ZBC) Hendriks & Roosenboom op.

Van 2005 tot 2008 was hij eerste geneeskundige binnen de ambulante volwassenenzorg van GGz-Nijmegen en sinds 2005 is hij tevens waarnemend A-opleider psychiatrie bij Forum GGz-Nijmegen. Van 2003 tot 2008 was hij secretaris van het Nederlands Kenniscentrum Angst en Depressie (www.nedkad.nl).

Sinds 2008 is hij directeur van het Centrum voor Angststoornissen 'Overwaal' in Lent/Nijmegen (Overwaal is een specialistisch behandelcentrum deel uitmakend van Forum GGz-Nijmegen). Binnen deze functie is hij betrokken bij het opzetten van een samenwerkingsverband met de afdeling klinische psychologie van de Radboud Universiteit Nijmegen op het gebied van angststoornissen (Nijmegen Centre for Anxiety Research and Expertise – NijCARE). Met ingang van 1 januari 2009 zijn Forum GGz-Nijmegen en De Gelderse Roos gefuseerd tot Pro Persona. Als directeur van Overwaal is hij medeverantwoordelijk voor de implementatie van het zorgprogramma angststoornissen in Pro Persona-verband.